BIOLOGICALLY ACTIVE INDOLE AND BISINDOLE ALKALOIDS FROM *LEUCONOTIS* AND *KOPSIA*

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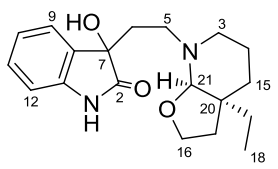
Abstract

Two Malaysian plants *viz.*, *Leuconotis griffithii* and *Kopsia pauciflora*, and one fungi strain (*Penicillium* sp. (CDA p48.3)) were investigated for their alkaloidal content and the results are summarized below (Table). A total of 107 alkaloids were isolated and characterized from these sources. Of these, 37 are new alkaloids. *Leuconotis griffithii* yielded a total of 24 new alkaloids, of which sixteen, *viz.*, the tetracyclic ring-opened oxindole leucolusine (**1**), the strychnan alkaloids, leuconicines A–G (**2–8**), the ring-C contracted rhazinilam alkaloid, *nor*-rhazinicine (**22**), the unprecedented eburnane–quinoline dimer, leucophyllidine (**36**), the eburnane–sarpagine bisindole, leuconoline (**37**), the aspidospermatan–aspidospermatan bisindole, leucofoline (**38**), and the *Strychnos*–*Strychnos* bisindoles, leucoridines A–D (**39**–**42**), are notable for incorporating novel or intriguing molecular skeletons. The stem-bark and leaf extracts of *Kopsia pauciflora* gave a total of 10 new alkaloids. These new alkaloids are the *seco*-leuconoxine alkaloid, compound **62**, the eburnane alkaloids, **63**–**64**, the corynanthean oxindole alkaloids, **69**–**71**, the corynanthean pseudoindoxyl alkaloid, tetrahydroalstonine pseudoindoxyl (**73**), the aspidofractinine alkaloid, 11,12-dimethoxykopsinaline (**77**), and the andransinine alkaloids, andransinine (**90**) and compound **91**. The culture broth extract of a *Penicillium* sp. (CDA p48.3) gave three new variotin derivatives, *viz.*, compounds **101**–**103**. Among the new alkaloids, 5,21-dihydrorhazinilam *N*-oxide (**23**), leucophyllidine (**36**), and leucoridine A (**39**) showed pronounced cytotoxic effects against human KB cells (IC_{50} 0.57–2.95 μg/mL), while leuconodine B (**10**), leuconodine D (**12**), *nor*-rhazinicine (**22**), leuconoline (**37**), leucofoline (**38**), and leucoridines B–D (**40**–**42**) showed only moderate to weak activity (IC_{50} 7.06–17.90 μg/mL). Leuconicines A–B (**2**–**3**), compound **70**, and andransinine

(**90**) were found to be effective in circumventing MDR in vincristine-resistant KB cells (IC_{50} 1.61–2.75 μg/mL), while leuconicines C–E (**4**–**6**), leuconodine E (**13**), and compounds **62**, **64**, and **91**, showed only moderate to weak activity (IC_{50} 3.86–18.13 μg/mL).

Abstrak (Versi Bahasa Malaysia)

Dua jenis tumbuhan dari Malaysia iaitu *Leuconotis griffithii*, dan *Kopsia pauciflora*, dan sejenis kulat (*Penicillium* sp. (CDA p48.3)) telah dikaji dari segi kandungan alkaloidnya, keputusan yang diperoleh telah dirumuskan di dalam jadual seperti di bawah. Sebanyak 107 alkaloid telah diasingkan dan dicirikan dari sumber yang dinyatakan di atas. Dari jumlah tersebut, 37 alkaloid merupakan alkaloid baru. Sebanyak 24 alkaloid baru telah diasingkan dari *Leuconotis griffithii*, antaranya, enam belas memiliki rangka karbon yang menarik, iaitu leucolusine (**1**), leuconicines A–G (**2–8**), *nor*-rhazinicine (**22**), leucophyllidine (**36**), leuconoline (**37**), leucofoline (**38**) dan leucoridines A–D (**39**–**42**). Ekstrak-ekstrak dari kulit-batang dan daun *Kopsia pauciflora* memberikan sejumlah 10 alkaloid baru. Alkaloid baru ini termasuklah sebatian **62**–**64**, **69**–**71**, tetrahydroalstonine pseudoindoxyl (**73**), 11,12-dimethoxykopsinaline (**77**), andransinine (**90**) dan sebatian **91**. Ekstrak dari supernatan *Penicillium* sp. (CDA p48.3) telah menghasilkan tiga terbitan baru variotin, iaitu sebatian **101**–**103**. Antara alkaloid baru ini, 5,21-dihydrorhazinilam *N*-oxide (**23**), leucophyllidine (**36**), dan leucoridine A (**39**), menunjukkan kesan sitotoksik yang kuat terhadap sel-sel KB (IC_{50} 0.57–2.95 μg/mL), manakala leuconodine B (**10**), leuconodine D (**12**), *nor*-rhazinicine (**22**), leuconoline (**37**), leucofoline (**38**), dan leucoridines B–D (**40**–**42**) menunjukkan kesan sitotoksik yang sederhana sahaja (IC_{50} 7.06–17.90 μg/mL). Leuconicines A–B (**2**–**3**), sebatian **70**, dan andransinine (**90**) memberikan kesan yang sangat kuat dalam memintasi ketahanan *multidrug* dalam sel-sel KB *vincristine-resistant* (IC_{50} 1.61–2.75 μg/mL), manakala leuconicines C–E (**4**–**6**), leuconodine E (**13**), dan sebatian **62**, **64**, dan **91**, hanya menunjukkan aktiviti yang sederhana sahaja (IC_{50} 3.86–18.13 μg/mL).



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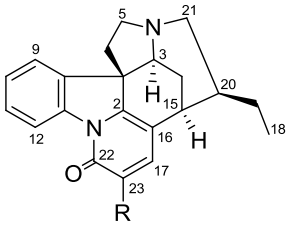
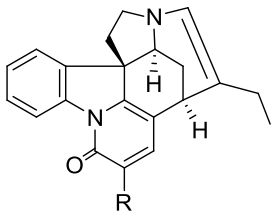
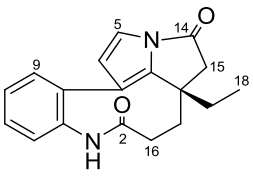


2 R = $CONH_2$
3 R = CO_2Me
7 R = $CONH_2$, *N*(4)→O
8 R = CO_2Me, *N*(4)→O



4 R = $CONH_2$
5 R = CO_2Me
6 R = COOH



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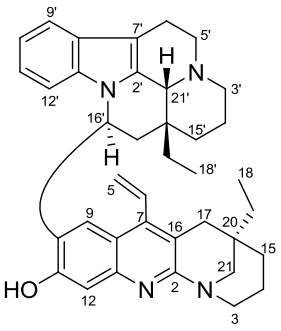

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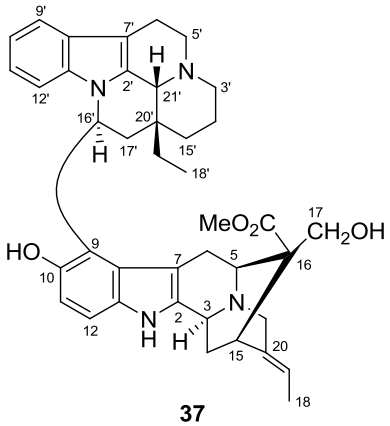

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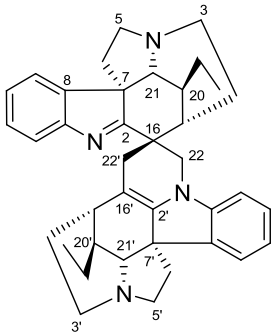

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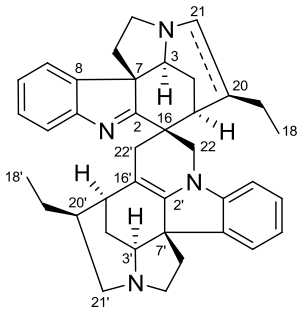

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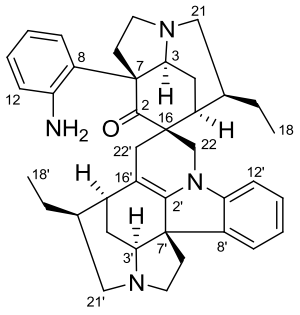
40 $\Delta^{20,21}$



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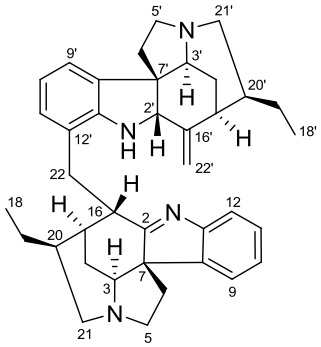

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Table: Alkaloid Composition of *L. griffithii*, *K. pauciflora*, and *Penicillium* sp. (CDA p48.3)

Plant	Plant part	Alkaloid
L. griffithii (Plant)	Stem-bark	Leucolusine (**1**) [New]
		Leuconicine A (**2**) [New]
		Leuconicine B (**3**) [New]
		Leuconicine C (**4**) [New]
		Leuconicine D (**5**) [New]
		Leuconicine E (**6**) [New]
		Leuconicine F (**7**) [New]
		Leuconicine G (**8**) [New]
		Leuconodine A (**9**) [New]
		Leuconodine B (scholarisine G) (**10**) [New]
		Leuconodine C (**11**) [New]
		Leuconodine D (**12**) [New]
		Leuconodine E (**13**) [New]
		Leuconoxine (**14**)
		Leuconodine F (6-oxoleuconoxine) (**15**)
		Mersicarpine (**16**)
		Arboloscine (**17**)
		3,14-Dehydroleuconolam (**18**) [New]
		Leuconolam (**19**)
		O-Methylleuconolam (**20**)
		Epi-leuconolam (**21**) or 6,7-dehydroleuconoxine (**21a**)
		Nor-rhazinicine (**22**) [New]
		5,21-Dihydrorhazinilam *N*-oxide (**23**) [New]
		5,21-Dihydrorhazinilam (**24**)
		Rhazinilam (**25**)
		Rhazinal (**26**)
		Rhazinicine (**27**)
		(−)-Eburnamaline (**28**) [New]
		(+)-Eburnamonine (**29**)
		(+)-Eburnamenine (**30**)
		O-Methylisoeburnamine (**31**)
		O-Methyleburnamine (**32**)
		(+)-Isoeburnamine (**33**)
		(−)-Eburnamine (**34**)
		(±)-Vincamine (**35**)
		Leucophyllidine (**36**) [New]
		Leuconoline (**37**) [New]
		Leucofoline (**38**) [New]
		Leucoridine A (**39**) [New]
		Leucoridine B (**40**) [New]
		Leucoridine C (**41**) [New]
		Leucoridine D (**42**) [New]
		Tetrahydroalstonine (**43**)
		17(*S*)-Ajmalicinial (**44**) and 17(*R*)-Ajmalicinial (**45**)
		Akuammidine (**46**)

Table, continued

Plant	Plant part	Alkaloid
		16(*R*)-19,20-*E*-Isositsirikine (**47**)
		16(*S*)-19,20-*E*-Isositsirikine (**48**)
		Z-Geissoschizol (**49**)
		Fluorocarpamine (**50**)
		Pleiocarpamine (**51**)
		16-Hydroxymethylpleiocarpamine (**52**)
		(–)-Isovallesiachotamine (**53**)
		(–)-Isovallesiachotamine (**53**) and (+)-Vallesiachotamine (**54**)
		Norfluorocurarine (**55**)
		12-Hydroxynorfluorocurarine (**56**)
		Tubotaiwine (**57**)
		Tubotaiwine *N*-oxide (**58**)
		N(4)-Chloromethyltubotaiwine chloride (**59**)
		Venoterpine (**60**)
		Syringaresinol (**61**)
K. pauciflora (Plant)	Stem-bark	Leuconoxine (**14**)
		Rhazinilam (**25**)
		Compound **63** [New]
		Compound **64** [New]
		(+)-Eburnamonine (**29**)
		(+)-Eburnamenine (**30**)
		(+)-Isoeburnamine (**33**)
		(–)-Eburnamine (**34**)
		19-Oxoeburnamine (**66**)
		(–)-19(*R*)-Hydroxyisoeburnamine (**67**)
		(+)-19(*R*)-Hydroxyeburnamine (**68**)
		Tetrahydroalstonine (**43**)
		11,12-Dimethoxykopsinaline (**77**) [New]
		Pseudokopsinine (**78**)
		Kopsinine (**79**)
		Kopsamine (**80**)
		N(1)-Decarbomethoxykopsamine (**81**)
		Kopsilongine (**82**)
		Paucifinine (**83**)
		Kopsanone (**84**)
		11,12-Methylenedioxykopsine (**85**)
		Kopsifine (**87**)
		N(1)-Decarbomethoxykopsifine (**88**)
		Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxy-chanofruticosinate (**95**)
		Methyl 11,12-methylenedioxychanofruticosinate (**96**)
		(–)-Norpleiomutine (**100**)
	Leaves	Compound **62** [New]
		Leuconoxine (**14**)
		Leuconodine F (6-oxoleuconoxine) (**15**)

Table, continued

Plant	Plant part	Alkaloid
		Mersicarpine (**16**)
		Leuconolam (**19**)
		Rhazinilam (**25**)
		Compound **63** [New]
		Larutenine (**65**)
		Compound **69** [New]
		Compound **70** [New]
		Compound **71** [New]
		(−)-Catharinensine (**72**)
		Tetrahydroalstonine pseudoindoxyl (**73**) [New]
		Tetrahydroalstonine (**43**)
		16(*R*)-19,20-*E*-Isositsirikine (**47**)
		(+)-Aspidospermidine (**74**)
		(+)-1,2-Dehydroaspidospermidine (**75**)
		(−)-Quebrachamine (**76**)
		Pseudokopsinine (**78**)
		Kopsinine (**79**)
		N(1)-Decarbomethoxykopsamine (**81**)
		Paucifinine (**83**)
		11,12-Methylenedioxykopsine (**85**)
		12-Methoxykopsine (**86**)
		Akuammicine (**89**)
		Andransinine (**90**) [New]
		Compound **91** [New]
		Condylocarpine (**92**)
		Precondylocarpine (**93**)
		Stemmadenine (**94**)
		Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxy-chanofruticosinate (**95**)
		Methyl 11,12-methylenedioxychanofruticosinate (**96**)
		Methyl chanofruticosinate (**97**)
		Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)
		Methyl 12-methoxychanofruticosinate (**99**)
Penicillium sp. (CDA p48.3) (Fungi)	Culture broth	Compound **101** [New]
		Compound **102** [New]
		Compound **103** [New]
		Variotin (**104**)
		Viriditin (**105**)
		cyclo (L-Phenylalanine-*trans*-4-hydroxy-L-proline) (**106**)
		cyclo (L-Leucine-*trans*-4-hydroxy-L-proline) (**107**)

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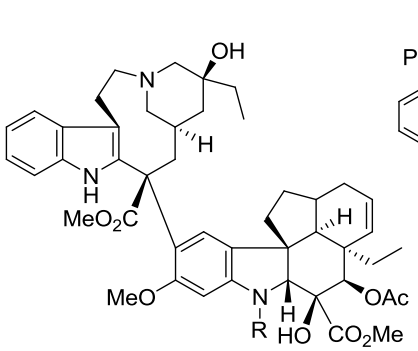
Chapter One

1 Introduction

1.1 General

Plants and microorganisms provide a diverse and unique source of secondary metabolites (also known as natural products), which are biosynthetically derived from primary metabolites.[1] The great majority of these substances do not participate directly in growth and development of an organism, and are often differentially distributed among limited taxonomic groups.[2-5] Since the study of natural products began in the 19th century,[6] organic chemists have shown great interest in the investigation of these phytochemicals for their chemical structures, biogenesis, and chemical synthesis. As chemical and biological techniques improved,[7-19] many complex chemical structures with intriguing skeletons were discovered from natural sources, and some of these substances were found to exhibit significant biological activities. In addition, an increasing number of natural product-based drugs were approved for therapeutic applications worldwide between 2005–2010.[20-23] Natural products have therefore proven to be fertile sources for the discovery of new biologically active agents, which provide useful lead compounds for drug discovery and development.[6,21,23-38] These therapeutic agents include the plant-derived agents, such as the *Vinca* alkaloids, vinblastine and vincristine,[39-46] paclitaxel (Taxol),[47-51] and camptothecin,[52-54] while those widely used as well as potential anticancer drugs of microbial origin include adriamycin (doxorubicin),[55-57] actinomycin,[58-61] bleomycins,[62-68] mitomycins,[69-72] and

epothilones.[73-76] Plants and microorganisms, therefore, represent a promising and still unexhausted source of potentially useful natural compounds. The rich natural resources available in this country[77] present the opportunity for finding new natural products of interest from the viewpoint of chemistry (structure, biogenesis, etc.) as well as biology (biological activity, etc.). Two plants of the Malayan Apocynaceae (*Leuconotis* and *Kopsia*) and one unidentified fungal strain (*Penicillium* sp.) were chosen for investigation in the present study with emphasis on the discovery and structure elucidation of new natural products, and the evaluation of biological activity.



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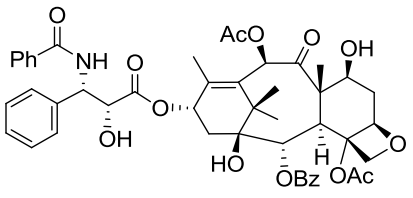
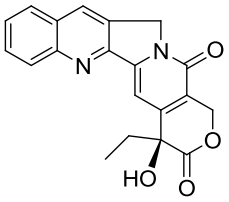
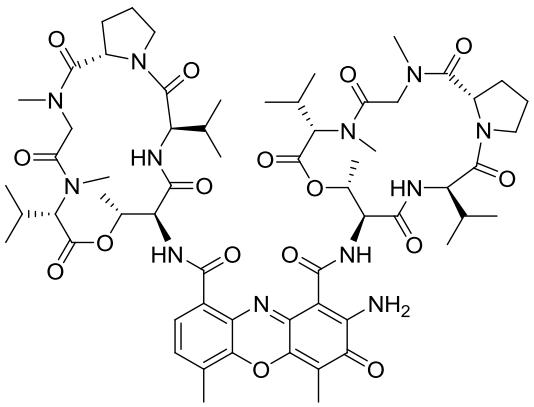
R = CHO vincristine



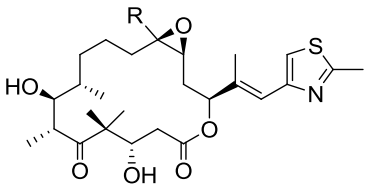
taxol



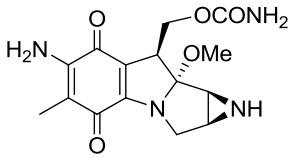
campthothecin



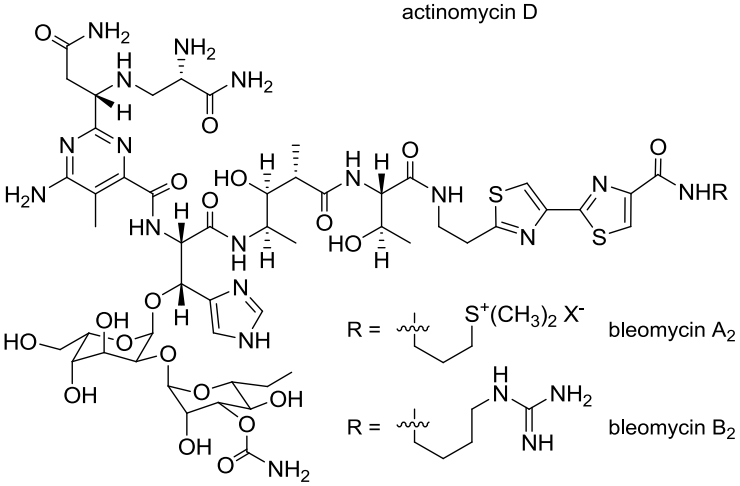
actinomycin D



R = H epothilone A
R = Me epothilone B



mitomycin C



R = $S^+(CH_3)_2$ X^- bleomycin A_2

R = bleomycin B_2

1.2 The Alkaloids

The isolation of morphine in 1805 by the German pharmacist, Friedrich Sertürner, marked the beginning of alkaloid chemistry. The term alkaloid, or 'alkali-like', was first proposed by another German pharmacist, W. Meissner in 1819. In 1983, S. W. Pelletier suggested a modern definition for alkaloids: An alkaloid is a cyclic compound containing nitrogen in a negative oxidation state which is of limited distribution in living organisms.[78-80] However, after many years of alkaloid research, this definition as such is no longer appropriate as it was found that alkaloids occur in all types of living organisms. Hesse has presented a new definition for alkaloids: Alkaloids are nitrogen-containing organic substances of natural origin with a greater or lesser degree of basic character.[78-80]

The total number of alkaloids so far isolated from various sources (plants, fungi, bacteria, marine organisms, mammals, *etc.*) is enormous.[81] These alkaloids can be classified based on the immediate environment of the N-atom in the individual alkaloid. Essentially, five distinct alkaloid classes were put forward according to the position of the N-atom in the main structural element:[78-80]

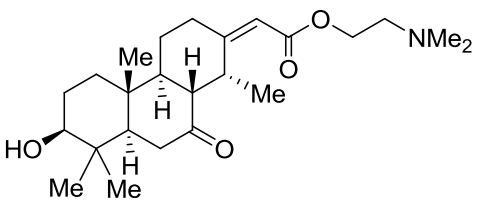
i. Heterocyclic alkaloids

ii. Alkaloids with exocyclic N-atoms and aliphatic amines (*e.g.*, cassaine, ephedrine)

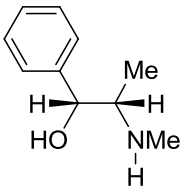
iii. Putrescine, spermidine, and spermine alkaloids (*e.g.*, paucine, inandenin-12-one, verbascenine)

iv. Peptide alkaloids (*e.g.*, integerrine, mucronine A)

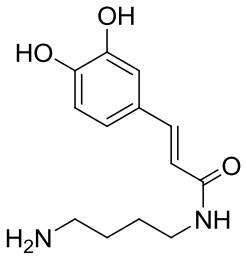
v. Terpene and steroid alkaloids (*e.g.*, atisine, veralkamine)



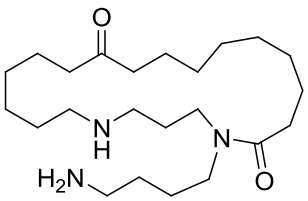
(–)-cassaine



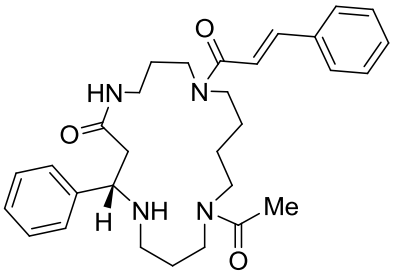
(–)-ephedrine



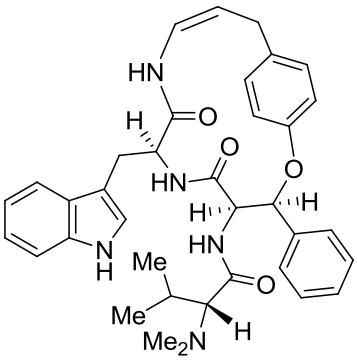
paucine



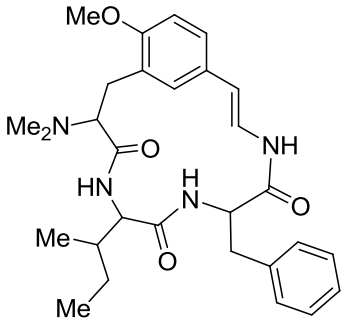
inandenin-12-one



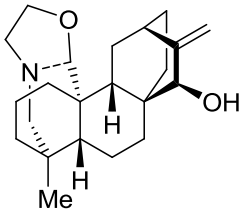
(–)-verbascenine



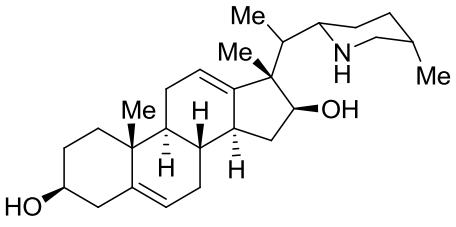
integerrine



mucronine A



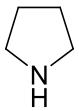
(–)-atisine



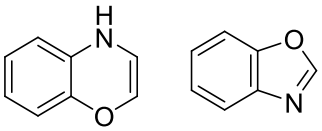
(–)-veralkamine

Among the five classes, the heterocyclic alkaloids constitute the largest group and in common usage, the term alkaloids usually refers to the heterocyclic alkaloids. These can be further divided into 15 subclasses based on the carbon-nitrogen skeleton as shown below:[78-80]

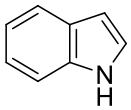
Pyrrolidine



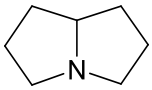
Benzoxazines and benzoxazoles



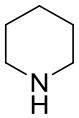
Indole



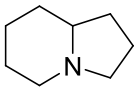
Pyrrolizidine



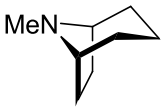
Piperidine



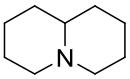
Indolizidine



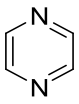
Tropane



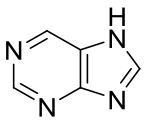
Quinolizidine



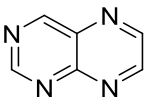
Pyrazine



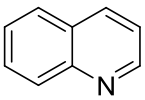
Purine



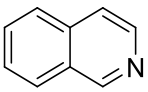
Pteridine



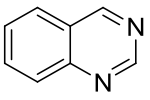
Quinoline



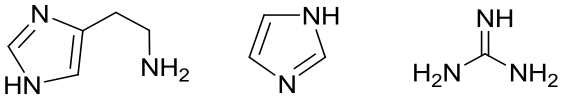
Isoquinoline



Quinazoline



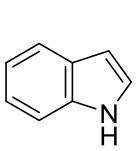
Histamine, imidazole, and guanidine



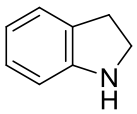
1.3 Indole Alkaloids of the Apocynaceae

1.3.1 General

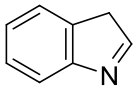
The indole alkaloids of Apocynaceae constitute one of the largest groups of alkaloids and account for about 20% of all known alkaloids.[78-81] This figure includes both those compounds that incorporate the actual indole chromophore and those containing its derivatives: namely indoline (dihydroindole), indolenine, hydroxyindolenine, α-methylideneindoline, pseudoindoxyl, and oxindole. Also members of this group are alkaloids in which the nucleus incorporates an additional benzene or pyridine ring, for instance, carbazole, or β- and γ-carbolines, and their derivatives.[78-80]



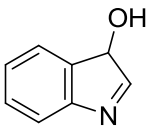
Indole



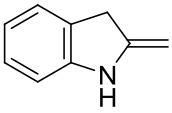
Indoline
or
Dihydroindole



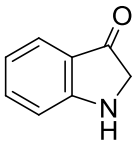
Indolenine



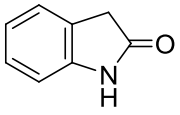
Hydroxyindolenine



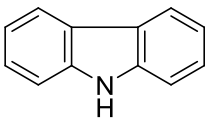
α-Methylideneindoline



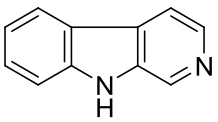
Pseudoindoxyl



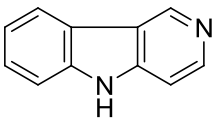
Oxindole



Carbazole



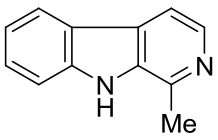
β-Carboline



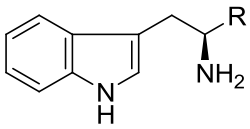
γ-Carboline

1.3.2 Classification of the Indole Alkaloids

The indole alkaloids are further subclassified according to their structural and biogenetic criteria. In general, the indole alkaloids can be divided into two main categories with respect to their structural features. The first comprises the simple indole alkaloids that do not present a structural uniformity, possessing only the indole nucleus or a direct derivative of it as a common feature (*e.g.*, harmane). Indole alkaloids of the second category, which are known as the monoterpene indole alkaloids, contain two structural units, *viz.*, tryptamine (or tryptophan) with the indole nucleus, and a C_9- or C_{10}-monoterpene moiety derived from secologanin. The majority of the indole alkaloids from plants are from this category.[78-80]

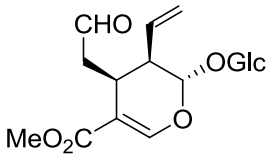


Harmane



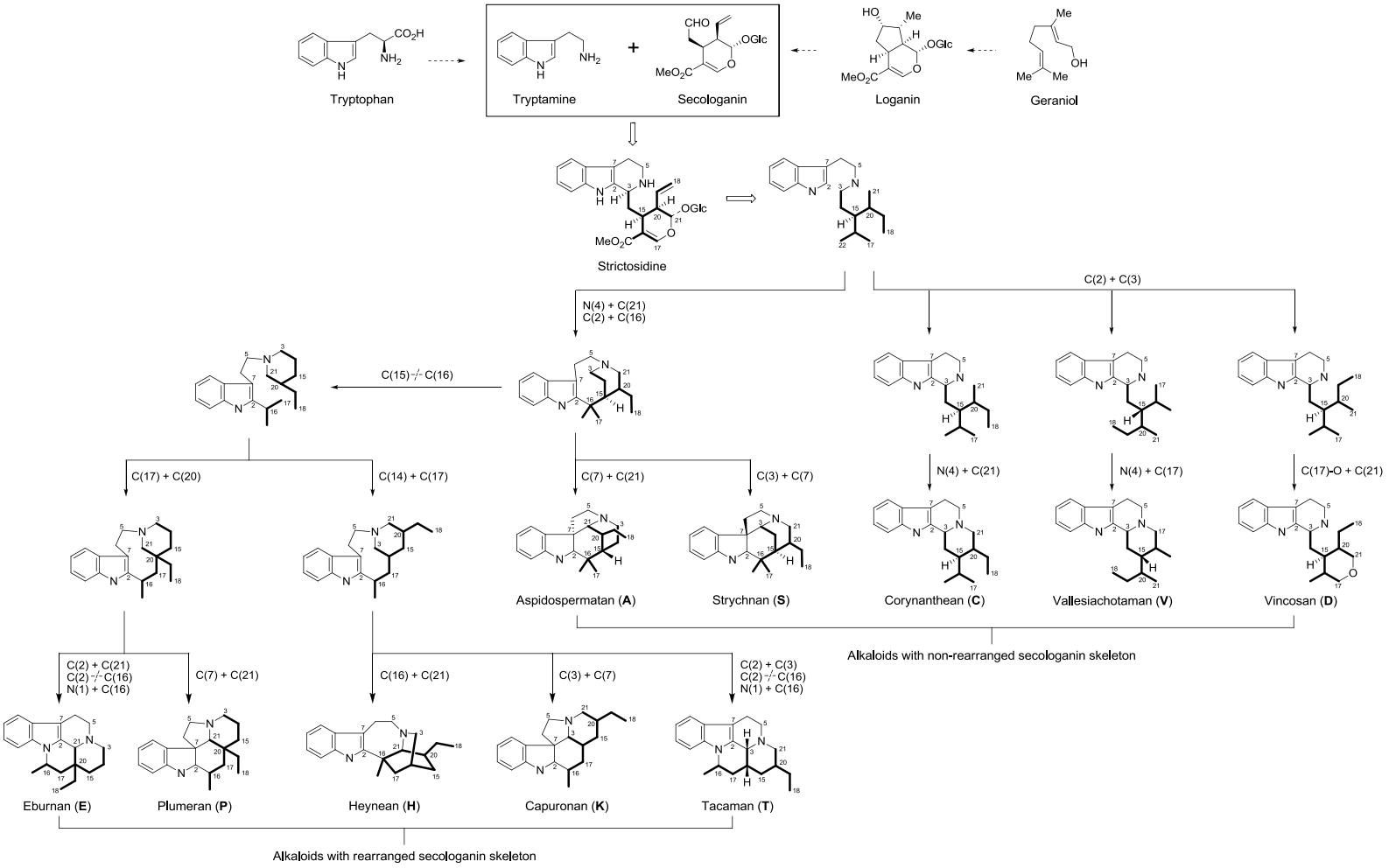
R = H Tryptamine

R = CO_2H Tryptophan

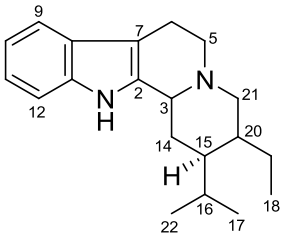
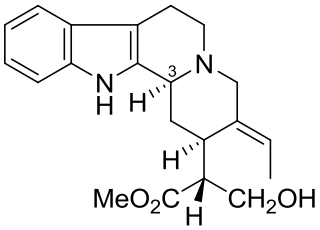
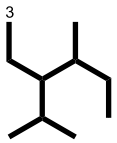
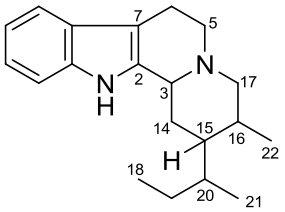
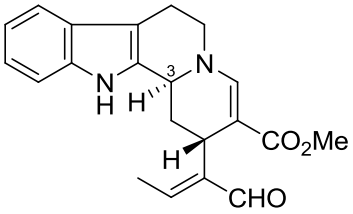
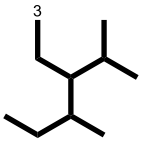
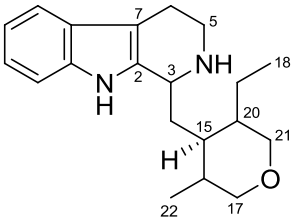
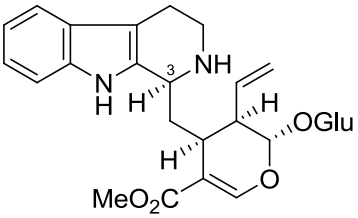
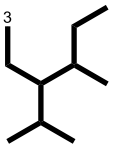
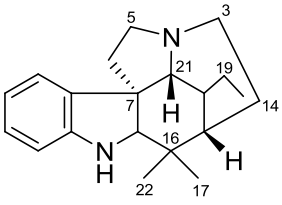
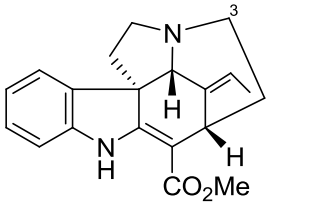
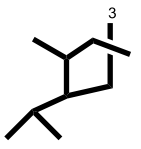
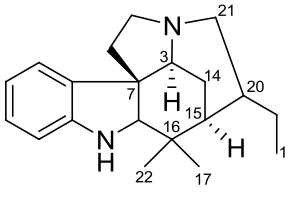
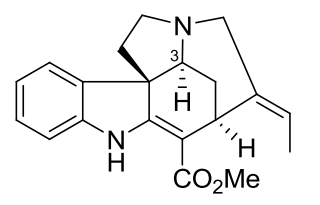


Secologanin

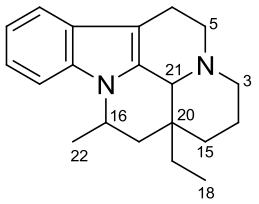
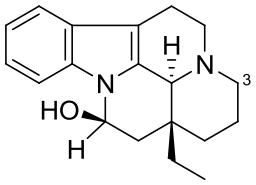
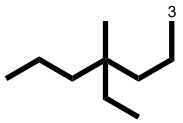
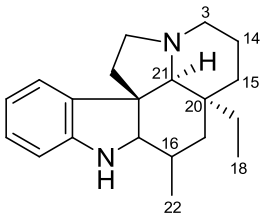
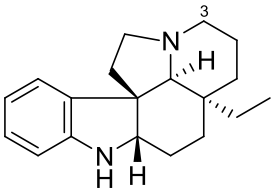
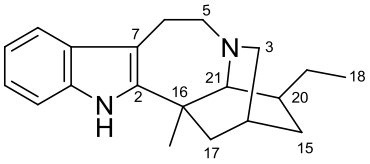
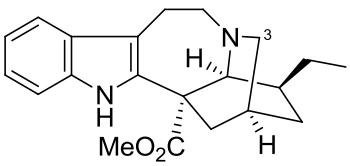
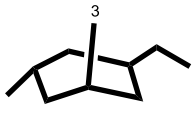
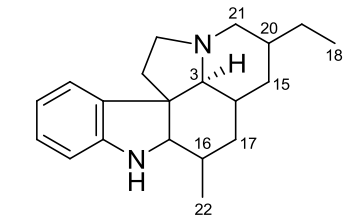
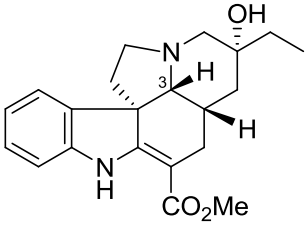
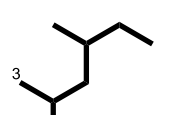
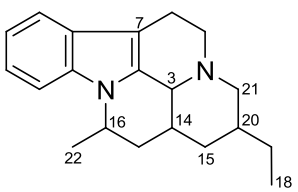
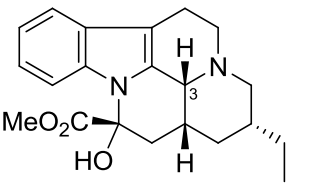
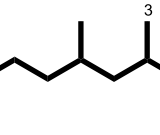
The monoterpene indole alkaloids shared a common precursor, namely strictosidine, which is a condensation product of secologanin and tryptamine.[82-84] Indole alkaloids can be grouped into ten main skeletal types: corynanthean (C), vincosan (D), vallesiachotaman (V), aspidospermatan (A), strychnan (S), eburnan (E), plumeran (P), heynean (H), capuronan (K), and tacaman (T).[85-116] Monoterpene indole alkaloids which do not present structural features that allow them to be accommodated in any of the ten main skeletal types considered above are listed as miscellaneous alkaloids. All indole alkaloids are biogenetically related and the biogenetic relationships of these alkaloids are given in Scheme 1.1.[78-80,108,112,114,116] The ten main skeletal types are given in Scheme 1.2.



Scheme 1.1: Biogenetic relationships of the ten main skeletal types of indole alkaloids

Alkaloid Type	Example	Skeleton of the C_9- or C_{10}- monoterpene unit
		
C-type	16(*R*)-19-*E*-Isositsirikine	
		
V-type	Vallesiachotamine	
		
D-type	Strictosidine	
		
A-type	Condylocarpine	
		
S-type	Akuammicine	

Scheme 1.2: Classification of indole alkaloids

Alkaloid Type	Example	Skeleton of the C_9- or C_{10}- monoterpene unit
		
E-type	(–)-Eburnamine	
		
P-type	Aspidospermidine	
		
H-Type	Coronaridine	
		
K-type	Pandoline	
		
T-type	Tacamine	

Scheme 1.2, continued

1.4 The Genus *Leuconotis*

1.4.1 General

The genus *Leuconotis* belongs to the tribe Willughbeieae, subfamily Rauvolfioideae of the family Apocynaceae. This genus occurs only in tropical Asia, mainly in southern Thailand, Indonesia and Peninsular Malaysia.[117-122] *Leuconotis* are usually woody climbers and all species have tetramerous flowers, which make this genus almost unique in the family. The leaves are usually petiolate, opposite to each other, blade elliptic or narrowly elliptic, with scattered black dots beneath, while the fruit is fleshy, indehiscent, subglobose or broadly pearshaped, and usually wrinkled when dried.[118,120]

Based on the most recent review of the genus by Middleton, a total of 4 species are recognized. The species are listed as follows:[118,120]

i. *L. anceps* Jack

ii. *L. bullata* Leeuwenb.

iii. *L. eugeniifolia* (Wall. ex G. Don) A. DC.

iv. *L. griffithii* Hook. f.

The latex from *L. eugeniifolia* has been used for the treatment of yaws and worm infections.[123]

1.4.2 Alkaloids of the Genus *Leuconotis*

The alkaloidal composition of the genus *Leuconotis* bears a striking similarity to that of the genus *Kopsia*.[77] Previous studies of the Malayan *L. griffithii* and *L. eugenifolia* provided kopsinine, eburnamine and a strychnan derivative (alkaloid 376), the ring-opened alkaloids leuconolam, *epi*-leuconolam, rhazinilam and their derivatives,[124-127] while two yohimbines and the pentacyclic diazaspiro alkaloid leuconoxine, were subsequently reported from *L. eugenifolia* occurring in Indonesia.[128] In addition to the indole alkaloids, ten new bisindole alkaloids (leucophyllidine, leuconoline, leucofoline, leucoridines A–D, leucoridine A *N*-oxide, bisleucocurine A, and bisleuconothine A) have also been recently reported.

1.4.3 Occurrence and Distribution of Alkaloids in the Genus *Leuconotis*

The occurrence of alkaloids in *Leuconotis* as reported in the literature (up to May 2012) is summarized in Table 1.1.

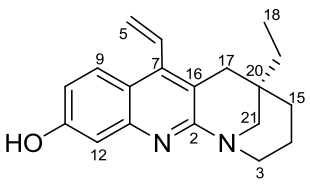
Table 1.1: Occurrence of Alkaloids in *Leuconotis*

Plant[a]	Plant part	Alkaloid	References
L. eugeniifolia	Leaves	Leuconolam (**19**)	128
(Wall. ex G. Don) A. DC.		Leuconoxine (**14**)	128
(*L. eugenifolius* DC.)		21-*O*-Methylleuconolam (**20**)	128
(Indonesia)		Rhazinaline *N*-oxide (**115**)	128
		Yohimbine (**116**)	128
		β-Yohimbine (**117**)	128
	Stem	Leuconolam (**19**)	128
		Leuconoxine (**14**)	128
		21-*O*-Methylleuconolam (**20**)	128
		Yohimbine (**116**)	128
		β-Yohimbine (**117**)	128

Table 1.1, continued

Plant[a]	Plant part	Alkaloid	References
L. eugeniifolia	Bark	Alkaloid 376 (= Leuconicine B) (**3**)[b]	124,126
(Wall. ex G. Don) A. DC.		5,21-Dihydrorhazinilam (**24**)[b]	124-126
(*L. eugenifolius* DC.)		Eburnamine (**34**)	124,126,127
(Peninsular Malaysia)		Eucophylline (**108**)	129
		Leuconolam (**19**)	124-127
		Epi-leuconolam (**21**)	124-126
		Leucophyllidine (**36**)[b]	129
		Rhazinilam (**25**)	124-126
L. griffithii Hook.f.	Leaves	Anhydropereirine (**110**)[b]	130,131
(*L. griffithii* (Retz.)		Bisleucocurine A (**120**)	130
Gardner ex Thwaites)		Leucomidine A (**111**)	132
		Leucomidine B (**112**)	132
		Leucomidine C (**113**)	132
		Leuconicine B (**3**)[b]	131
		Leucoridine A (**39**)[b]	131
		Leucoridine A *N*-oxide (**119**)	131
		Melohenine A (**114**)[b]	131
	Stem-bark	Bisleuconothine A (**118**)	133
		(+)-Eburnamenine (**30**)	133
L. griffithii Hook.f.	Stem-bark	5,21-Dihydrorhazinilam (**24**)[b, c]	124-126
		(–)-Eburnamaline (**28**)[c]	134
		(+)-Eburnamenine (**30**)[c]	134
		(–)-Eburnamine (**34**)[c]	124,126,127,134
		(+)-Eburnamonine (**29**)[c]	134
		(+)-Isoeburnamine (**33**)[c]	134
		Kopsinine (**79**)[b]	124,126
		Leucofoline (**38**)[c]	135
		Leucolusine (**1**)[c]	136
		Leuconicine A (**2**)[c]	134
		Leuconicine B (= Alkaloid 376) (**3**)[c]	124,126,134
		Leuconicine C (**4**)[c]	134
		Leuconicine D (**5**)[c]	134
		Leuconicine E (**6**)[c]	134
		Leuconicine F (**7**)[c]	134
		Leuconicine G (**8**)[c]	134
		Leuconolam (**19**)[c]	124-127
		Epi-leuconolam (**21**)[c]	124-126
		Leuconoline (**37**)[c]	135
		Leucophyllidine (**36**)[c]	137
		Leucoridine A (**39**)[c]	138
		Leucoridine B (**40**)[c]	138
		Leucoridine C (**41**)[c]	138
		Leucoridine D (**42**)[c]	138
		O-Methyleburnamine (**32**)[c]	124,126,127
		O-Methylisoeburnamine (**31**)[c]	124,126,127
		Norfluorocurarine (**55**)[b, c]	124,126,127
		Norfluorocurarine *N*-oxide (**109**)[b]	124,126,127
		Rhazinilam (**25**)[c]	124-126

[a] Classification according to Middleton[120] with original attribution in parenthesis; [b] $[\alpha]_D$ not reported; [c] Compounds isolated from present study.



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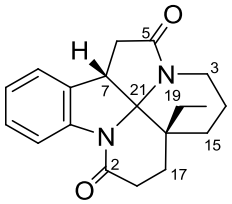

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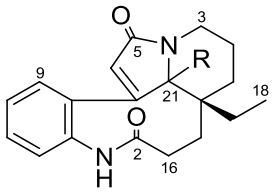
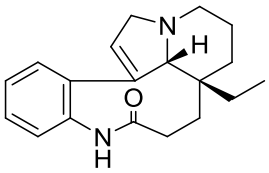


19 R = β-OH
20 R = β-OMe
21 R = α-OH



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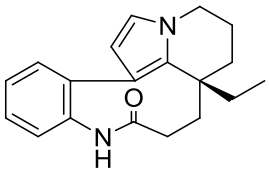

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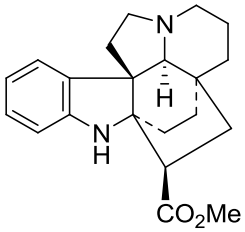

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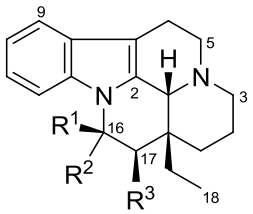
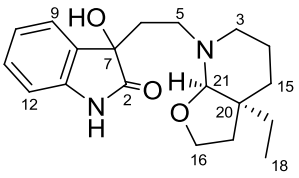
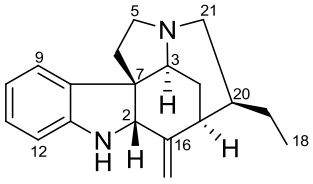


28 $R^1 = R^3 = OH$, $R^2 = H$
29 R^1, $R^2 = O$, $R^3 = H$
30 $R^1 = R^3 = H$, R^2 = nil $\Delta^{16,17}$
31 $R^1 = R^3 = H$, $R^2 = OMe$
32 $R^1 = OMe$, $R^2 = R^3 = H$
33 $R^1 = R^3 = H$, $R^2 = OH$
34 $R^1 = OH$, $R^2 = R^3 = H$



1



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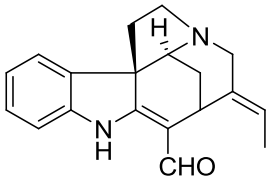
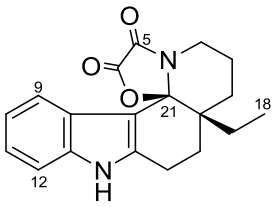


55
109 N(4)→O



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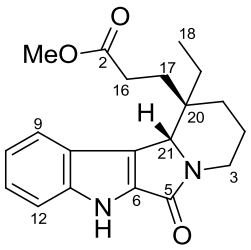

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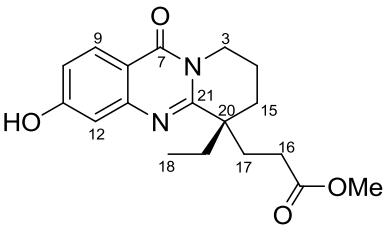

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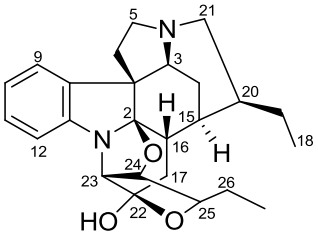

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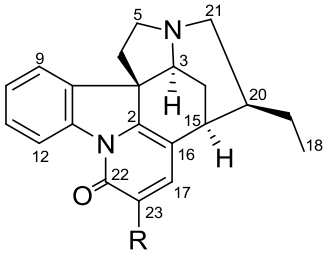
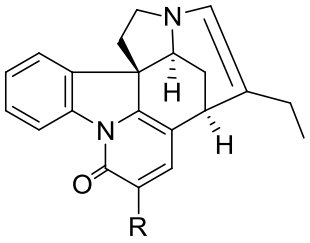
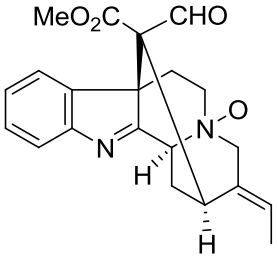


2 R = $CONH_2$
3 R = CO_2Me
7 R = $CONH_2$, N(4)→O
8 R = CO_2Me, N(4)→O



4 R = $CONH_2$
5 R = CO_2Me
6 R = COOH



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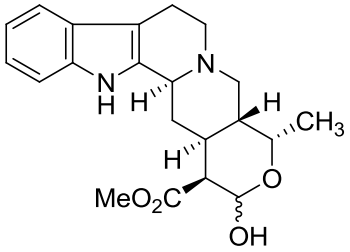
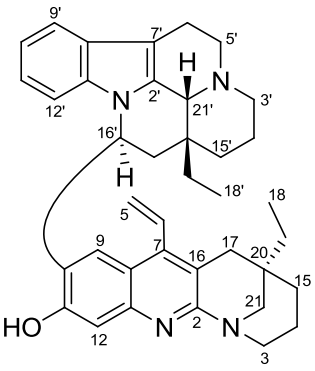


116 17*S*
117 17*R*



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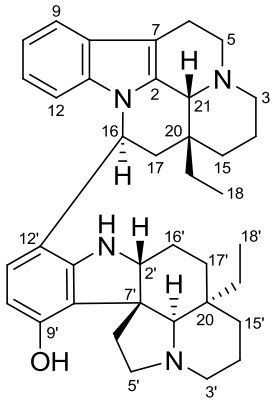

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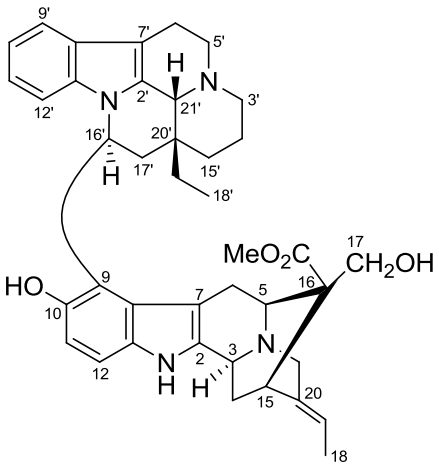

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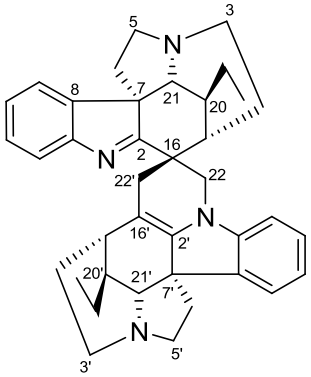

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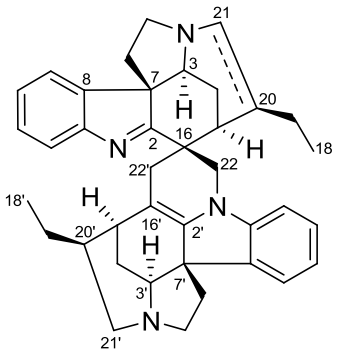
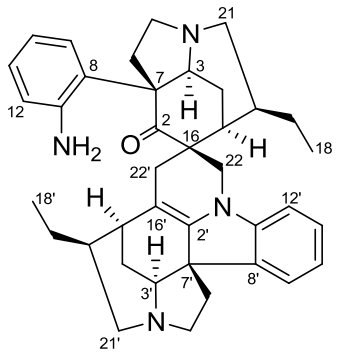


39
40 $\Delta^{20,21}$
119 N(4)→O



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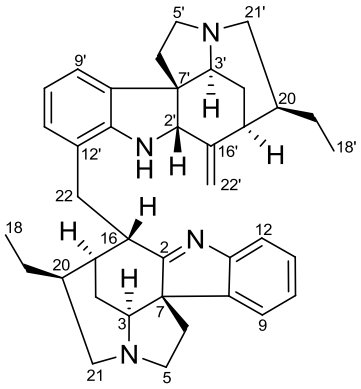

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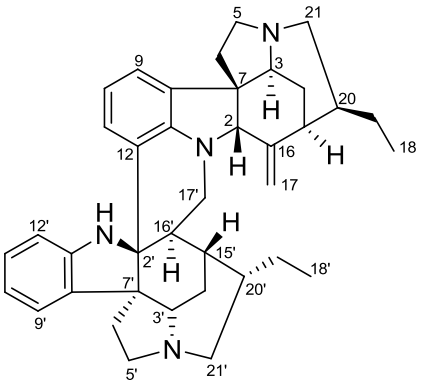


120

1.5 The Genus *Kopsia*

1.5.1 General

The genus *Kopsia* belongs to the tribe Vinceae, subfamily Rauvolfioideae of the family Apocynaceae.[139,140] This genus is widely distributed in South East Asia[141-143] and is most diverse in Peninsular Malaysia and Sarawak.[140] A few species are found in China, India, and Australia.[141-143]

All *Kopsia* species are shrubs or small trees, occurring as part of the understory vegetation in forests, at forest edges, or in the open. Most of the species have young branchlets, and in some species the angles become so pronounced as to become wing-like. The leaves are usually opposite to each other, and mostly petiolate. All species have a small to large gland right below the apex of the sepal. A unique peculiarity of most species of this genus is the nose-like ventral appendage of the mericarp which is a cavity completely secluded from the seed-bearing portion by a wall.[140,144,145]

In the most recent revision of the genus by Middleton, a total of 24 species are recognized, two of which have two varieties each.[140,146] Eighteen species occur in Peninsular Malaysia, while four are found in Malaysian Borneo (Sabah and Sarawak).[145] They are listed as follows:[140,145]

i. *K. arborea* Blume

ii. *K. dasyrachis* Ridl.

iii. *K. deverrei* L. Allorge

iv. *K. fruticosa* (Roxb.) A. DC.

v. *K. grandifolia* D. J. Middleton

vi. *K. griffithii* King & Gamble var. *griffithii*

vii. *K. griffithii* King & Gamble var. *pubescens* D. J. Middleton

viii. *K. larutensis* King & Gamble

ix. *K. macrophylla* Hook. f.

x. *K. pauciflora* Hook. f. var. *pauciflora*

xi. *K. pauciflora* Hook. f. var. *mitrephora* (Sleesen) D. J. Middleton

xii. *K. profunda* Markgr.

xiii. *K. rajangensis* D. J. Middleton

xiv. *K. rosea* D. J. Middleton

xv. *K. singapurensis* Ridl.

xvi. *K. sleeseniana* Markgr.

xvii. *K. tenuis* Leenh. & Steenis

xviii. *K. teoi* L. Allorge

In Malaysia, the roots of *K. larutensis*, *K. pauciflora*, *K. profunda* (*K. macrophylla*), and *K. singapurensis* are used for poulticing ulcerated noses in tertiary syphilis.[145] Under the name ‘somu’, *K. flavida* is used as a contraceptive in Vanuatu.[145] While in China, *K.*

arborea (*K. officinalis*) was used for the treatment of rheumatoid arthritis and gout.[147,148]

1.5.2 Alkaloids of the Genus *Kopsia*

Plants of the genus *Kopsia* have proven to be prodigious sources of indole alkaloids with alkaloids of the aspidofractinine skeletal type predominating (Table 1.2). In addition to the known bisindoles, *viz.*, kopsoffinol, (−)-norpleiomutine, (–)-demethylnorpleiomutine, (+)-kopsoffine, tenuiphylline, nitaphylline, and the quasidimer buchtienine, a new bisindole of the corynanthe–aspidospermatan type, kopsiyunnanine A, was recently isolated from the aerial part of a *Kopsia* species.[149] Several monoterpene alkaloids related to skytanthine (kinabalurines A–G, kopsilactone, and kopsone) have also been isolated from a few *Kopsia* species.[145,150]

1.5.3 Occurrence and Distribution of Alkaloids in the Genus *Kopsia*

The occurrence of alkaloids in *Kopsia* as reported in the literature (up to May 2012) is summarized in Table 1.2.

Table 1.2: Occurrence of Alkaloids in *Kopsia*

Plant[a]	Plant part	Alkaloid	References
K. arborea Blume (Peninsular Malaysia)	Leaves	Arbophylline (**137**)	151
		Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)	152
		Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (**95**)	152
		Methyl 11,12-methylenedioxychanofruticosinate (**96**)	152
		Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxy-$\Delta^{14,15}$-chanofruticosinate (**308**)	152
		Prunifoline A (**296**)	153
		Prunifoline B (**297**)	153
		Prunifoline C (**298**)	153
		Prunifoline D (**299**)	153
		Prunifoline E (**300**)	153
		Prunifoline F (**301**)	153
	Stem-bark	Akuammidine (**46**)	154,155
		Arboflorine (**134**)	154-156
		Arboloscine (**17**)	155,157
		Arboricine (**135**)	155,158
		Arboricinine (**136**)	155,158
		Aspidofractinine (**200**)	155
		Dasyrachine (**313**)	155
		N(1)-Decarbomethoxykopsamine (**81**)	155
		5,21-Dihydrorhazinilam (**24**)	155
		15α-Hydroxykopsinine (**190**)	155
		Kopsamidine A (**192**)	155
		Kopsamidine B (**193**)	155
		Kopsamine (**80**)	155
		Kopsamine *N*-oxide (**213**)	155
		Kopsanone (**84**)	155
		Kopsifine (**87**)	155
		Kopsiflorine (**215**)	155
		Kopsilongine (**82**)	155
		Kopsinidine A (**277**)	155
		Kopsinidine B (**278**)	155
		Kopsinine (**79**)	155
		Leuconoxine (**14**)	155
		Mersicarpine (**16**)	155,159
		N(1)-Methoxycarbonyl-11,12-dimethoxykopsinaline (= 11-Methoxykopsilongine) (**218**)	155
		19(*S*)-Methoxytubotaiwine (**161**)	155
		19(*R*)-Methoxytubotaiwine (**162**)	155
		Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)	155
		11,12-Methylenedioxykopsine (**85**)	155
		O-Methylleuconolam (**20**)	155
		Methyl 12-methoxychanofruticosinate (**99**)	155
		Methyl 11,12-methylenedioxychanofruticosinate (**96**)	155
		Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (**95**)	155
		Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxy-$\Delta^{14,15}$-chanofruticosinate (**308**)	155
		Norfluorocurarine (**55**)	155
		Paucidactine B (**275**)	155

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
		Paucidactine C (**276**)	155
		Pericidine (**158**)	155,157
		Pericine (**159**)	155
		Pericine *N*-oxide (**160**)	155
		Pleiocarpamine (**51**)	155
		Prunifoline E (**300**)	155
		Rhazimal (**144**)	155
		Rhazinicine (**27**)	155
		Rhazinilam (**25**)	155
		Rhazinoline (**143**)	155
		Tetrahydroalstonine (**43**)	155
		Valparicine (**157**)	155,160
		Venalstonidine (**202**)	155
		Venalstonine (**201**)	155
		Vincadifformine (**186**)	155
K. arborea Blume (*K. flavida*) (Peninsular Malaysia)	Leaves	Danuphylline B (**320**)	161
		Flavisiamine A (= Prunifoline D) (**299**)	162
		Flavisiamine B (**303**)	162
		Flavisiamine C (= Prunifoline F) (**301**)	162
		Flavisiamine D (= Prunifoline E) (**300**)	162
		Flavisiamine E (**304**)	162
		Flavisiamine F (**309**)	162
		12-Methoxykopsine (**86**)	161
		Methyl 11,12-dimethoxychanofruticosinate (**305**)	163
		Methyl 11,12-methylenedioxy-*N*(1)-decarbo-methoxychanofruticosinate (**95**)	163
		Methyl 12-methoxychanofruticosinate (**99**)	163
		Methyl 12-methoxy-*N*(1)-decarbomethoxy-chanofruticosinate (**306**)	163
		Methyl 3-oxo-11,12-methylenedioxy-*N*(1)-decarbo-methoxy-14,15-didehydrochanofruticosinate (**311**)	164
		Methyl 3-oxo-12-methoxy-*N*(1)-decarbomethoxy-14,15-didehydrochanofruticosinate (**312**)	164
		Prunifoline C (**298**)	162
K. arborea Blume (*K. albiflora*, *K. pruniformis*) (India)	Leaves	Kopsine (**279**)	165-168
K. arborea Blume (*K. jasminiflora*) (Thailand)	Leaves	14,15-Dehydrokopsijasminilam (**329**)	169
		10-Demethoxykopsidasinine (**323**)	170
		Deoxykopsijasminilam (**328**)	169
		Fruticosamine (**282**)	169
		Fruticosine (**281**)	169
		Jasminiflorine (**284**)	169
		Kopsijasmine (**255**)	169
		Kopsijasminilam (**327**)	169

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
K. arborea Blume (*K. longiflora*) (Queensland, Australia)	Leaves	Kopsamine (**80**)	171,172
		Kopsiflorine (**215**)	171,172
		Kopsilongine (**82**)	171,172
	Stem-bark	Kopsamine (**80**)	171,172
		Kopsilongine (**82**)	171,172
		Kopsinine (**79**)	171,172
K. arborea Blume (*K. pitardii*) (Vietnam)	Leaves	Methyl 11,12-methylenedioxy-*N*(1)-decarbo-methoxy-$\Delta^{14,15}$-chanofruticosinate (**308**)	173
		Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)	173
		Methyl 11,12-methylenedioxychanofruticosinate (**96**)	173
K. arborea Blume (*K. officinalis*) (China)	Leaves	11,12-De(methylenedioxy)danuphylline (**319**)	174
		(+)-Eburnamonine (**29**)	174
		16β-Hydroxyaspidofractinine (**211**)	174
		(−)-19(*R*)-Hydroxyisoeburnamine (**67**)	174
		(+)-19(*R*)-Hydroxyeburnamine (**68**)	174
		(+)-Isoeburnamine (**33**)	174
		Kopsamine (**80**)	174
		Kopsiflorine (**215**)	174
		Kopsilongine (**82**)	174
		Kopsinine (**79**)	174
		Kopsinine *N*-oxide (**189**)	174
		Kopsininic acid (**203**)	174
		Larutenine (= Larutensine) (**65**)	174
		11-Methoxykopsilongine (**218**)	174
		12-Methoxykopsinaline (**222**)	174
		Methyl 11,12-methylenedioxychanofruticosinate (**96**)	174,175
		Methyl chanofruticosinate (**97**)	174,175
		Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)	175
		Methyl *N*(1)-decarbomethoxy-$\Delta^{14,15}$-3-oxo-chanofruticosinate (**310**)	174
		Rhazinicine (**27**)	174
	Leave-twigs	Methyl 5-oxo-chanofruticosinate (**302**)	176
	Roots	5,22-Dioxokopsane (**287**)	147
		(−)-Isoeburnamine (**172**)	147,177
		Kopsinine (**79**)	147,177
		(+)-Kopsoffine (**376**)	177
		N(1)-Methoxycarbonyl-11,12-dimethoxykopsinaline **(**= 11-Methoxykopsilongine**)** (**218**)	147
		N(1)-Methoxycarbonyl-12-methoxykopsinaline (= kopsilongine) (**82**)	147
		N(1)-Methoxycarbonyl-11,12-methylenedioxy-kopsinaline (= kopsamine) (**80**)	147
		12-Methoxykopsinaline (**222**)	147
		11,12-Methylenedioxykopsinaline (**81**)	147
		(−)-Quebrachamine (**76**)	147
		Tetrahydroalstonine (**43**)	147

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
	Aerial	Arboloscine (**17**)	178
		Condylocarpine (**92**)	149,179
		Condylocarpine *N*-oxide (**166**)	179
		Eburenine (**187**)	180
		(+)-Eburnamenine (**30**)	180
		(−)-Eburnamine (**34**)	180
		(+)-Eburnamonine (**29**)	180
		(−)-Ethyleburnamine (= *O*-Ethyleburnamine) (**174**)	180
		(+)-Ethylisoeburnamine (= *O*-Ethylisoeburnamine) (**175**)	180
		Isocondylocarpine (**168**)	179
		Isocondylocarpine *N*-oxide (**169**)	179
		(+)-Isoeburnamine (**33**)	180
		Kopsiyunnanine A (**381**)	149
		Kopsiyunnanine B (**133**)	149
		Kopsiyunnanine C1 (= 5-Methoxymethylrhazinilam) (**183**)	178
		Kopsiyunnanine C2 (= 5-Ethoxymethylrhazinilam) (**184**)	178
		Kopsiyunnanine C3 (=5-Hydroxymethylrhazinilam) (**185**)	178
		Kopsiyunnanine D (**180**)	178
		Kopsiyunnanine F1 (= 19*S*,20*R*-Epoxy-tubotaiwine) (**163**)	179
		Kopsiyunnanine F2 (= 19*R*,20*R*-Epoxy-tubotaiwine) (**164**)	179
		Kopsiyunnanine F3 (= 19*R*,20*S*-Epoxy-tubotaiwine) (**165**)	179
		Kopsiyunnanine G (**188**)	180
		Kopsiyunnanine H (**181**)	180
		Mersicarpine (**16**)	178
		19(*S*)-Methoxytubotaiwine (**161**)	179
		19(*R*)-Methoxytubotaiwine (**162**)	179
		(−)-Methyleburnamine (= *O*-Methyleburnamine) (**32**)	180
		(+)-Methylisoeburnamine (= *O*-Methyl-isoeburnamine) (**31**)	180
		(−)-Quebrachamine (**76**)	178
		Rhazinilam (**25**)	178
		Tetrahydroalstonine (**43**)	149
		Tubotaiwine (**57**)	149
	Fruits	*N*(1)-Carbomethoxy-11,12-dimethoxykopsinaline (= 11-Methoxykopsilongine) (**218**)	181
		N(1)-Carbomethoxy-11-hydroxy-12-methoxy-kopsinaline (**221**)	181
		N(1)-Carbomethoxy-11-methoxy-12-hydroxy-kopsinaline (**217**)	181
		N(1)-Carbomethoxy-12-methoxykopsinaline (**82**)	181
		5,22-Dioxokopsane (**287**)	181
		Eburnamenine[b]	181
		Kopsamine (**80**)	181
		Kopsamine *N*-oxide (**213**)	181
		Kopsanone (**84**)	181

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
		Kopsinilam (**191**)	181
		Kopsinine (**79**)	181
		Pleiocarpine (**197**)	181
		Vincadifformine (**186**)	181
	c	Eburnamine[b]	148
		Kopsinine (**79**)	148
		Kopsamine (**80**)	148
		Perivine (**142**)	148
		19-Hydroxyeburnamine[b]	148
		19-Oxoeburnamenine (**176**)[b]	148
		19-Oxoeburnamine[b]	148
K. arborea Blume (Indonesia)	Leaves	Flavisiamine A (= Prunifoline D) (**299**)	182
		Flavisiamine C (= Prunifoline F) (**301**)	182
		Flavisiamine D (= Prunifoline E) (**300**)	182
		Kopreasin A (**307**)	182
		Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)	182
		Methyl 12-methoxychanofruticosinate (**99**)	182
		Methyl 12-methoxy-*N*(1)-decarbomethoxy-chanofruticosinate (**306**)	182
		Methyl 11,12-methylenedioxychanofruticosinate (**96**)	182
		Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (**95**)	182
		Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxy-$\Delta^{14,15}$-chanofruticosinate (**308**)	182
		Prunifoline B (**297**)	182
K. dasyrachis Ridl. (Sabah, Malaysian Borneo)	Leaves	Danuphylline (**318**)	183-185
		11,12-Dimethoxykopsamine (= 11-Methoxy-kopsilongine) (**218**)	183
		Kinabalurine G (**127**)	183
		Kopsamine (**80**)	183
		Kopsamine *N*-oxide (**213**)	183
		Kopsidasine (**258**)	186
		Kopsidasine *N*-oxide (**259**)	186
		Kopsidasinine (**321**)	186
		Kopsifine (**87**)	183
		Kopsirachine (**130**)	183,187
		12-Methoxypleiocarpine (**194**)	183
		Methyl chanofruticosinate (**97**)	183
		Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)	183
		Methyl 11,12-methylenedioxychanofruticosinate (**96**)	183
		Methyl 11,12-methylenedioxy-*N*(1)-decarbo-methoxychanofruticosinate (**95**)	183
		Pleiocarpine (**197**)	183
	Stem-bark	*N*(1)-Carbomethoxy-5,22-dioxokopsane (**288**)	188
		Dasyrachine (**313**)	188
		Decarbomethoxykopsifine (**88**)	188
		(–)-Demethylnorpleiomutine (**377**)	188

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
		(+)-Eburnamonine (**29**)	188
		(–)-19(*R*)-Hydroxyisoeburnamine (**67**)	188,189
		(+)-19(*R*)-Hydroxyeburnamine (**68**)	188,189
		16-Hydroxymethylpleiocarpamine (**52**)	188
		(+)-Isoeburnamine (**33**)	188
		Kopsamine (**80**)	188
		Kopsamine *N*-oxide (**213**)	188
		Kopsifine (**87**)	188,190
		Kopsiflorine (**215**)	188
		Kopsiflorine *N*-oxide (**216**)	188
		Kopsilongine (**82**)	188
		Kopsinarine (**285**)	188
		Kopsine (**279**)	188
		Kopsinine (**79**)	188
		Kopsinine *N*-oxide (**189**)	188
		(+)-Kopsoffinol (**378**)	188
		Leuconoxine (**14**)	188
		11-Methoxykopsilongine (**218**)	188
		11-Methoxykopsilongine *N*-oxide (**220**)	188
		12-Methoxypleiocarpine (**194**)	188
		11,12-Methylenedioxykopsinaline (**81**)	188
		11,12-Methylenedioxykopsine (**85**)	188
		(–)-Norpleiomutine (**100**)	188
		Paucidactine B (**275**)	188
		Pleiocarpamine (**51**)	188
		Pleiocarpine (**197**)	188
		Rhazinicine (**27**)	188,190
		Tetrahydroalstonine (**43**)	188
K. deverrei L. Allorge (Peninsular Malaysia)	Leaves	14,15-Dihydro-10-methoxykopsinone (**208**)	191
		10-Methoxykopsinone (**206**)	191
		12-Methoxykopsinone (**207**)	191
	Stem-bark	*N*(1)-Carbomethoxy-17β-hydroxykopsinine (**195**)	192
		N(1)-Carbomethoxy-17β-hydroxy-$\Delta^{14,15}$-kopsinine (**196**)	192
		Deacetylakuammiline (= Rhazimol) (**145**)	193
		16-*Epi*-deacetylakuammiline (**148**)	193
		14α-Hydroxycondylocarpine (**167**)	193
		16-Hydroxymethylpleiocarpamine (**52**)	193
		N(1)-Methoxycarbonyl-11,12-methylenedioxy-kopsinaline (**80**)	192
		N(1)-Methoxycarbonyl-12-methoxykopsinaline	192
		Kopsinone (**205**)	192
		Pleiocarpamine (**51**)	193
K. fruticosa (Roxb.) A. DC. (India, Indonesia, Malaysia)	Leaves	Fruticosamine (**282**)	141,162,194-196
		Fruticosiamine A (**283**)	162
		Fruticosine (**281**)	141,162,194-196

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
		Kopsine (**279**)	141,162,195-202
		Decarbomethoxykopsine (**280**)	202
		Decarbomethoxyisokopsine (**314**)	202
		Methyl decarbomethoxychanofruticosinate (**98**)	162
K. grandifolia D. J. Middleton (*K. lapidilecta*) (Peninsular Malaysia)	Stem-bark	*Epi*-lapidilectinol (**338**)	203
		Isolapidilectine A (**335**)	203
		Lapidilectam (**336**)	203
		Lapidilectine A (**334**)	203,204
		Lapidilectine B (**343**)	203
		Lapidilectinol (**337**)	203
		Venalstonine (**201**)	203
	Leaves	Lapidilectine B (**343**)	203,204
	Stem-bark[d]	Grandilodine A (**331**)	205
		Grandilodine B (**332**)	205
		Isolapidilectine A (**335**)	205
		Kopsinine (**79**)	205
		Lapidilectam (**336**)	205
		Lapidilectine A (**334**)	205
	Leaves[d]	Grandilodine C (**333**)	205
		Lapidilectine B (**343**)	205
K. griffithii King & Gamble (Peninsular Malaysia)	Leaves	Buchtienine (**380**)	206
		N(1)-Carbomethoxy-11,12-dimethoxy-kopsinaline (= 11-Methoxykopsilongine) (**218**)	206
		N(1)-Carbomethoxy-11-hydroxy-12-methoxy-kopsinaline (**221**)	206
		(+)-Eburnamonine (**29**)	206
		Epi-leuconolam (**21**)	207
		Harmane (**131**)	206
		(+)-Harmicine (**132**)	206
		16(*R*)-19,20-*E*-Isositsirikine (**47**)	206
		Kopsamine (**80**)	206
		Kopsamine *N*-oxide (**213**)	206
		Kopsilongine (**82**)	206
		Kopsinine (**79**)	206
		Leuconolam (**19**)	206
		Leuconoxine (**14**)	206
		N(1)-Methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine (**261**)	206
		12-Methoxy-10-demethoxykopsidasinine (**322**)	206
		12-Methoxypleiocarpine (**194**)	206
		6-Oxoleuconoxine (**15**)	208
		Pleiocarpine (**197**)	206
		Rhazimol (= Deacetylakuammiline) (**145**)	206
		Tetrahydroalstonine (**43**)	206

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
	Stem-bark	Akuammiline *N*-oxide (**149**)	209
		Buchtienine (**380**)	209
		Deacetylakuammiline (= Rhazimol) (**145**)	209
		(−)-Eburnamine (**34**)	209
		16-*Epi*-deacetylakuammiline (**148**)	209
		16-*Epi*-deacetylakuammiline *N*-oxide (**150**)	209
		Harmane (**131**)	209
		Kopsinine (**79**)	209
		Kopsinine *N*-oxide (**189**)	209
		Leuconolam (**19**)	209
		Leuconoxine (**14**)	209
		11,12-Methylenedioxykopsinaline *N*-oxide (**214**)	209
		Rhazinaline *N*-oxide (**115**)	209
K. hainanensis Tsiang (China)	Leaves-stems	Kopsihainanine A (**315**)	210
		Kopsihainanine B (**316**)	210
	Stem-bark	5,22-Dioxokopsane (**287**)	211
		Eburnamenine[b]	211
		(+)-Eburnamine (**171**)	211
		(−)-Isoeburnamine (**172**)	211
		Kopsihainin A (**317**)	212
		Kopsihainin B (**198**)	212
		Kopsihainin C (**199**)	212
		Kopsanone (**84**)	211
		Kopsinilam (**191**)	211
		Kopsinine (**79**)	211,212
		Kopsininic acid (**203**)	211
		Kopsinoline (= Kopsinine *N*-oxide) (**189**)	211
		(+)-Kopsoffine (**376**)	211
		Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)	212
		(+)-Tubotaiwine (**57**)	211
	Twigs-leaves	Kopsinine (**79**)	213
		Tubotaiwine (**57**)	213
K. larutensis King & Gamble (Peninsular Malaysia)	Leaves	(−)-Eburnamine (**34**)	214
		(+)-Eburnamonine (**29**)	214
		(+)-Eburnamonine *N*-oxide (**173**)	214
		(+)-Isoeburnamine (**33**)	214
		(+)-Larutenine/larutensine (**65**)	214
	Stem-bark	(+)-Eburnamenine (**30**)	215
		(−)-Eburnamine (**34**)	215,216
		(−)-Eburnaminol (**177**)	216
		(+)-Eburnamonine (**29**)	215,216
		(+)-Eburnamonine *N*-oxide (**173**)	215
		(−)-*O*-Ethyleburnamine (**174**)	215
		(+)-Isoeburnamine (**33**)	215,216
		Kopsinine (**79**)	215,216
		(+)-Larutensine/larutenine (**65**)	215,216

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
K. pauciflora Hook.f. (Sabah, Malaysian Borneo)	Leaves	Kinabalurine A (**121**)	217,218
		Kinabalurine B (**122**)	218
		Kinabalurine C (**123**)	218
		Kinabalurine D (**124**)	218
		Kinabalurine E (**125**)	218
		Kinabalurine F (**126**)	218
		Kopsamine (**80**)	219
		Kopsamine *N*-oxide (**213**)	219
		Lahadinine A (**225**)	220
		Lahadinine B (**226**)	220
		11-Methoxykopsilongine (**218**)	219
		Paucidactine A (**274**)	221
		Paucidactine B (**275**)	221
		Paucifinine (**83**)	220
		Paucifinine *N*-oxide (**224**)	220
		Pauciflorine A (**324**)	222
		Pauciflorine B (**325**)	222
		Pauciflorine C (**326**)	219
		Paucifoline (**330**)	219
	Stem-bark	(−)-Demethylnorpleiomutine (**377**)	223
		(−)-Eburnamine (**34**)	224
		(+)-Eburnamonine (**29**)	224
		(+)-Isoeburnamine (**33**)	224
		Kopsamine *N*-oxide (**213**)	224
		Kopsinine (**79**)	224
		(+)-Kopsoffine (**376**)	223
		(+)-Kopsoffinol (**378**)	223
		N(1)-Methoxycarbonyl-11,12-dimethoxykopsinaline (= 11-Methoxykopsilongine) (**218**)	224
		N(1)-Methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine (**261**)	224
		N(1)-Methoxycarbonyl-12-methoxykopsinaline (= kopsilongine) (**82**)	224
		N(1)-Methoxycarbonyl-11,12-methylenedioxy-kopsinaline (= kopsamine) (**80**)	224
		12-Methoxy-10-demethoxykopsidasinine (**322**)	224
		(−)-Norpleiomutine (**100**)	223,224
		(+)-19-Oxoeburnamine (**66**)	224
		Pauciflorine A (**324**)	219
K. profunda (Peninsular Malaysia)	Leaves and stem-bark	Kopsinine (**79**)	225
		N(1)-Methoxycarbonyl-12-hydroxy-$\Delta^{16,17}$-kopsinine (**262**)	225
		N(1)-Methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine (**261**)	225,226
		N(1)-Methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine *N*-oxide (**264**)	225
		N(1)-Methoxycarbonyl-11,12-methylenedioxy-$\Delta^{16,17}$-kopsinine (**260**)	225,226
		N(1)-Methoxycarbonyl-11,12-methylenedioxy-$\Delta^{16,17}$-kopsinine *N*-oxide (**263**)	225

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
K. profunda Markgr. (*K. macrophylla*) (Peninsular Malaysia)	Leaves	Kopsilactone (**128**)	227
		Kopsone (**129**)	227
	Stem-bark	Akuammiline (**146**)	227
		Deacetylakuammiline (**145**)	227
		5,22-Dioxokopsane (**287**)	227
		Dregamine (**138**)	227
		(+)-Kopsoffine (**376**)	227
		Norpleiomutine (**100**)	227
		Tabernaemontanine (**139**)	227
K. profunda Markgr. (*K. terengganensis*) (Peninsular Malaysia)	Stem-bark	(–)-Eburnamine (**34**)	228
		(–)-Eburnaminol (**177**)	228
		(+)-Isoeburnamine (**33**)	228
		(+)-Larutensine (**155**)	228
		(+)-Quebrachamine (**182**)	228
		Terengganensine A (**178**)	228
		Terengganensine B (**179**)	228
K. singapurensis Ridl. (1) (Sample A)[e] (Peninsular Malaysia)	Leaves	16-*Epi*-akuammiline (**147**)	229
		16-*Epi*-deacetylakuammiline (**148**)	229
		16-*Epi*-kopsinine (**204**)	229
		Kopsidine D (**269**)	229
		Kopsilongine (**82**)	229
		Kopsilongine *N*-oxide (**219**)	229
		Kopsiloscine A (**228**)	229
		Kopsiloscine B (**229**)	229
		Kopsiloscine C (**230**)	229
		Kopsiloscine D (**231**)	229
		Kopsiloscine E (**232**)	229
		Kopsiloscine F (**233**)	229
		Kopsingine (**237**)	229
		Vincophylline (**140**)	229
	Stem-bark	Akuammidine (**46**)	229
		Aspidodasycarpine (**151**)	229
		Aspidophylline A (**152**)	229
		16-*Epi*-akuammiline (**147**)	229
		16-*Epi*-deacetylakuammiline (**148**)	229
		17α-Hydroxy-$\Delta^{14,15}$-kopsinine (**227**)	229
		Kopsaporine (**238**)	229
		Kopsinganol (**246**)	229
		Kopsingine (**237**)	229
		Kopsinine (**79**)	229
		Leuconolam (**19**)	229
		Lonicerine (**154**)	229
		Rhazinal (**26**)	229,230
		Rhazinilam (**25**)	229
		Tetrahydroalstonine (**43**)	229

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
K. singapurensis Ridl. (2) (Sample B)[e] (Peninsular Malaysia)	Leaves	Akuammidine (**46**)	231
		16-*Epi*-akuammiline (**147**)	231
		16-*Epi*-deacetylakuammiline (**148**)	231
		Kopsidarine (**247**)	231
		Kopsidine A (**265**)	231
		Kopsidine C (**267**)	231
		Kopsidine C *N*-oxide (**268**)	231
		Kopsimaline F (**253**)	231
		Kopsinganol (**246**)	231
		Kopsingine (**237**)	231
		Kopsinitarine A (**289**)	231
		Kopsinitarine B (**290**)	231
		Mersingine A (**294**)	231
	Stem-bark	Akuammidine (**46**)	231
		Aspidodasycarpine (**151**)	231
		Aspidophylline B (**153**)	231
		5,21-Dihydrorhazinilam (**24**)	231
		16-*Epi*-akuammiline (**147**)	231
		16-*Epi*-deacetylakuammiline (**148**)	231
		17α-Hydroxy-$\Delta^{14,15}$-kopsinine (**227**)	231
		Kopsiloscine C (**230**)	231
		Kopsiloscine G (**234**)	231
		Kopsinganol (**246**)	231
		Kopsingine (**237**)	231
		Kopsinine (**79**)	231
		Lonicerine (**154**)	231
		Rhazinilam (**25**)	231
K. singapurensis Ridl. (3) (*K. fruticosa*) (Peninsular Malaysia)	Leaves	Akuammidine (**46**)	232
		N(1)-Decarbomethoxykopsamine (**81**)	232
		5,21-Dihydrorhazinilam (**24**)	232
		16-*Epi*-akuammiline (**147**)	232
		16-*Epi*-deacetylakuammiline (**148**)	232
		17α-Hydroxy-$\Delta^{14,15}$-kopsinine (**227**)	232
		Kopsiloscine G (**234**)	232
		Kopsiloscine J (**245**)	232
		Kopsimaline A (**248**)	232
		Kopsimaline B (**249**)	232
		Kopsimaline C (**250**)	232
		Kopsimaline D (**251**)	232
		Kopsimaline E (**252**)	232
		Kopsinicine (**244**)	232
		Kopsofinone (**210**)	232
		Mersinine A (**354**)	233,234
		Mersinine B (**355**)	233,234
		Mersinine C (**356**)	234
		Mersiloscine (**357**)	233,234
		Mersiloscine A (**358**)	234
		Mersiloscine B (**359**)	234
		Mersifoline A (**360**)	234
		Mersifoline B (**361**)	234

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
		Mersifoline C (**362**)	234
		Mersidasine A (**363**)	234
		Mersidasine B (**364**)	234
		Mersidasine C (**365**)	234
		Mersidasine D (**366**)	234
		Mersidasine E (**367**)	234
		Mersidasine F (**368**)	234
		Mersidasine G (**369**)	234
		Mersiphylline A (**370**)	235,236
		Mersiphylline B (**371**)	235,236
		Mersilongine (**374**)	232,237
		Mersirachine (**372**)	232,238
		Mersinaline (**373**)	232,238
		Rhazinilam (**25**)	232
	Stem-bark	Akuammidine (**46**)	232
		Aspidodasycarpine (**151**)	232
		Burnamine (**155**)	232
		Deacetylakuammiline (**145**)	232
		5,21-Dihydrorhazinilam (**24**)	232
		16-*Epi*-akuammiline (**147**)	232
		16-*Epi*-deacetylakuammiline (**148**)	232
		14α-Hydroxycondylocarpine (**167**)	232
		16-Hydroxymethylpleiocarpamine (**52**)	232
		Kopsiloscine H (**235**)	232
		Kopsiloscine I (**236**)	232
		Kopsinine (**79**)	232
		Leuconolam (**19**)	232
		Leuconoxine (**14**)	232
		Lonicerine (**154**)	232
		Mersicarpine (**16**)	159,232
		Mossambine (**170**)	232
		Picramicine (**156**)	232
		Rhazinilam (**25**)	232
		Tetrahydroalstonine (**43**)	232
K. singapurensis Ridl. (4) (*K. fruticosa*) (Peninsular Malaysia)	Leaves	15α-Hydroxykopsinine (**190**)	239
		Kopsifoline A (**348**)	239-241
		Kopsifoline B (**349**)	239-241
		Kopsifoline C (**350**)	239-241
		Kopsifoline D (**351**)	239,241
		Kopsifoline E (**352**)	239,241
		Kopsifoline F (**353**)	239,241
		Kopsorinine (**286**)	239
		Venacarpine A (**256**)	239
		Venacarpine B (**257**)	239
	Stem-bark	Akuammigine (**141**)	239
		16-*Epi*-deacetylakuammiline (**148**)	239
		16-*Epi*-kopsinine (**204**)	239
		15α-Hydroxykopsinine (**190**)	239
		16-Hydroxymethylpleiocarpamine (**52**)	239

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
		Kopsanone (**84**)	239
		Kopsinine (**79**)	239
		Kopsorinine (**286**)	239
		Lonicerine (**154**)	239
		Picramicine (**156**)	239
		Pleiocarpamine (**51**)	239
		Venalstonine (**201**)	239
K. singapurensis Ridl. (5) (Peninsular Malaysia)	Leaves	5,21-Dihydrorhazinilam (**24**)	242,243
		Kopsifoline A (**348**)	244
		Kopsininic acid (**203**)	244
		11,12-Methylenedioxykopsaporine (**241**)	242,243
		Rhazinilam (**25**)	242,243
		Singaporentine A (**347**)	244
	Stem-bark	11,12-Methylenedioxykopsaporine (**241**)	242
		Singapurensine A (**270**)	242
		Singapurensine B (**271**)	242
		Singapurensine C (**272**)	242
		Singapurensine D (**273**)	242
K. singapurensis Ridl. (6) (Peninsular Malaysia)	Leaves	Kopsaporine (**238**)	245,246
		Kopsingine (**237**)	245,246
K. tenuis Leenh. & Steenis (Sarawak, Malaysian Borneo)	Leaves	Lundurine A (**339**)	247,248
		Lundurine B (**340**)	247,248
		Lundurine C (**341**)	247,248
		Lundurine D (**342**)	247
		Tenuiphylline (**379**)	249
		Tenuisine A (**344**)	247,249,250
		Tenuisine B (**345**)	247,249,250
		Tenuisine C (**346**)	247,249,250
	Stem	Kopsinine (**79**)	219
		Kopsinine *N*-oxide (**189**)	219
		Leuconoxine (**14**)	219
		Tetrahydroalstonine (**43**)	219
K. teoi L. Allorge (1) (Peninsular Malaysia)	Leaves	11-Hydroxykopsingine (**239**)	251
		Kopsidine A (**265**)	251-253
		Kopsidine B (**266**)	251-253
		Kopsidine C (**267**)	251,253
		Kopsidine D (**269**)	251,253
		14,15-α-Epoxykopsingine (= Kopsimaline E) (**252**)	251
		Kopsinganol (**246**)	251,252
		Kopsingine (**237**)	251,252
		Kopsinitarine A (**289**)	251,254,255

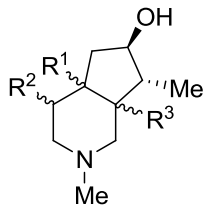
Table 1.2, continued

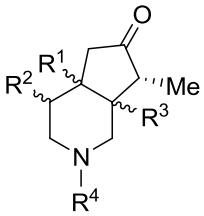
Plant[a]	Plant part	Alkaloid	References
		Kopsinitarine B (**290**)	251,254,255
		Kopsinitarine C (**291**)	251,254,255
		Kopsinitarine D (**292**)	251,255
		Mersingine A (**294**)	251,254,256
		Mersingine B (**295**)	251,254,256
		11-Methoxy-12-hydroxykopsinol (**243**)	251
		11-Methoxykopsingine (**240**)	251
		Nitaphylline (**375**)	251,257,258
	Stem-bark[e]	Akuammiline (**146**)	251,252,259
		Aspidodasycarpine (**151**)	251
		16-*Epi*-deacetylakuammiline (**148**)	251
		17α-Hydroxy-$\Delta^{14,15}$-kopsinine (**227**)	251,252,257,259,260
		Kopsaporine (**238**)	251,252,259,260
		Kopsinganol (**246**)	251,252,259
		Kopsingine (**237**)	251,252,259,260
		Kopsinginine (**223**)	251,252,259,260
		Kopsinginol (**212**)	251,252,259
		Kopsinol (**242**)	251,252,259
		Lonicerine (**154**)	251
		11,12-Methylenedioxykopsaporine (**241**)	251
		Rhazimol (= Deacetylakuammiline) (**145**)	251,252,259
		Rhazinilam (**25**)	251,252,259
K. teoi L. Allorge (2) (Peninsular Malaysia)	Stem-bark[e]	Akuammiline (**146**)	208
		Aspidodasycarpine (**151**)	208
		Deacetylakuammiline (= Rhazimol) (**145**)	208
		16-*Epi*-akuammiline (**147**)	208
		16-*Epi*-deacetylakuammiline (**148**)	208
		16-*Epi*-kopsinine (**204**)	208
		17α-Hydroxykopsinine (= Kopsiloscine G) (**234**)	208
		16-Hydroxymethylpleiocarpamine (**52**)	208
		Kopsamine (**80**)	208
		Kopsidine A (**265**)	208
		Kopsijasminine (**254**)	208
		Kopsinganol (**246**)	208
		Kopsingine (**237**)	208
		Kopsinine (**79**)	208
		Kopsinitarine E (**293**)	208
		Kopsonoline (**209**)	208
		Leuconoxine (**14**)	208
		Lonicerine (**154**)	208
		N(1)-Methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine (**261**)	208
		Pleiocarpamine (**51**)	208
		Tetrahydroalstonine (**43**)	208

Table 1.2, continued

Plant[a]	Plant part	Alkaloid	References
K. teoi L. Allorge (3) (Peninsular Malaysia)	Leaves	Kopsingine (**237**)	261
		11,12-Methylenedioxykopsaporine (**241**)	261
	Stem-bark	17α-Hydroxy-$\Delta^{14,15}$-kopsinine (**227**)	261
		Isoeburnamine[b]	261
		Kopsingine (**237**)	261
		Lonicerine (**154**)	261
		Rhazinilam (**25**)	261

[a] Classification according to Middleton[140] with original attribution in parenthesis; [b] $[\alpha]_D$ not reported; [c] Plant part not specified; [d] Reinvestigation of plant material collected at same location and same dates; [e] Plant material collected at same location but at different dates.





121 R^1 = β-H, R^2 = α-Me, R^3 = α-H

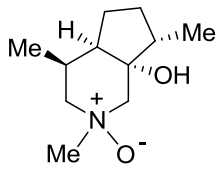
125 R^1 = α-H, R^2 = β-Me, R^3 = β-H

126 R^1 = α-H, R^2 = α-Me, R^3 = β-H

122 R^1 = β-H, R^2 = α-Me, R^3 = α-H, R^4 = Me

123 R^1 = β-H, R^2 = α-Me, R^3 = α-H, R^4 = H

124 R^1 = α-H, R^2 = β-Me, R^3 = β-H, R^4 = Me



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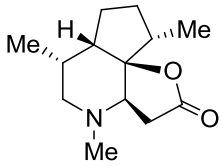

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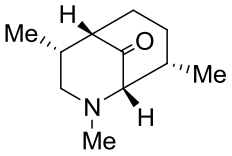

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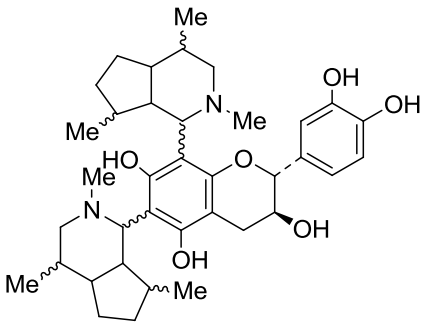

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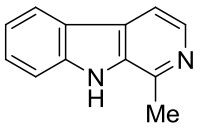

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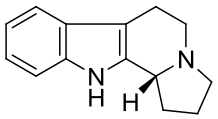

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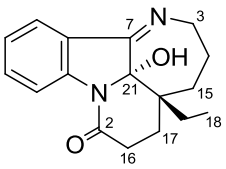

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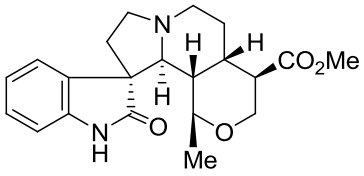

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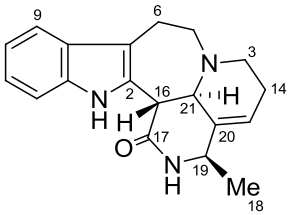

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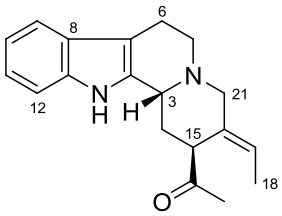

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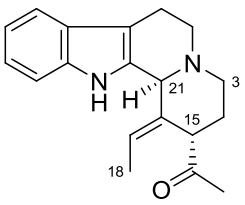

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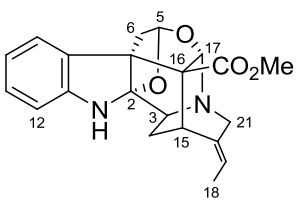

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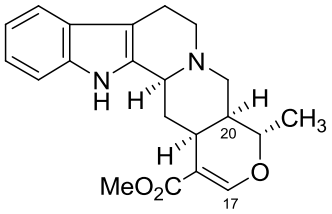

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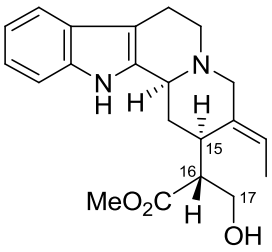

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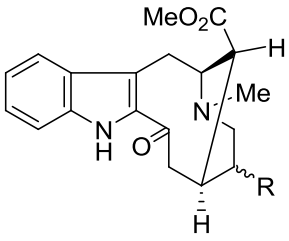
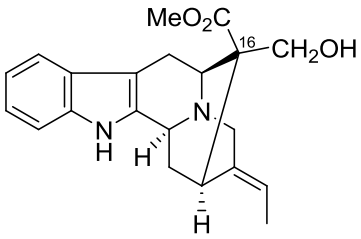


138 R = α-Et
139 R = β-Et



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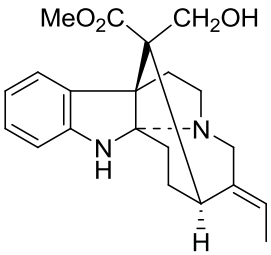

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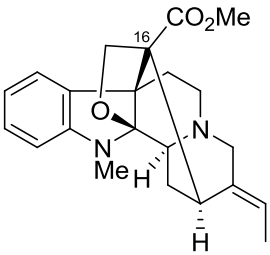

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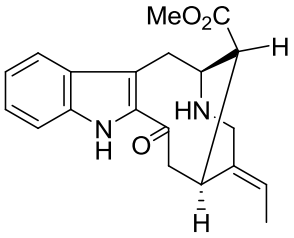
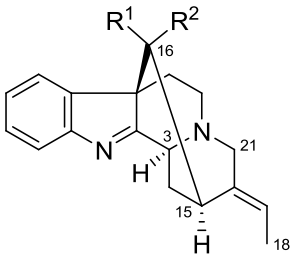
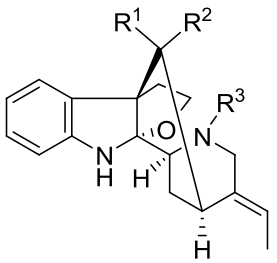


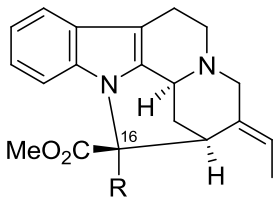
142



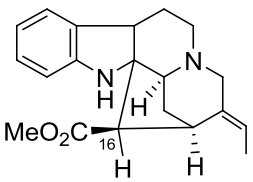
115 $R^1 = CO_2Me$, R^2 = CHO, N(4)→O
143 R^1 = CHO, R^2 = H
144 $R^1 = CO_2Me$, R^2 = CHO
145 $R^1 = CH_2OH$, $R^2 = CO_2Me$
146 $R^1 = CH_2OAc$, $R^2 = CO_2Me$
147 $R^1 = CO_2Me$, $R^2 = CH_2OAc$
148 $R^1 = CO_2Me$, $R^2 = CH_2OH$
149 $R^1 = CH_2OAc$, $R^2 = CO_2Me$, N(4)→O
150 $R^1 = CO_2Me$, $R^2 = CH_2OH$, N(4)→O



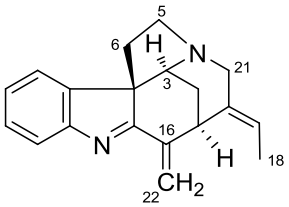
151 $R^1 = CH_2OH$, $R^2 = CO_2Me$, R^3 = H
152 R^1 = H, $R^2 = CO_2Me$, R^3 = CHO
153 $R^1 = CH_2OAc$, $R^2 = CO_2Me$, R^3 = H
154 $R^1 = CO_2Me$, $R^2 = CH_2OH$, R^3 = H
155 $R^1 = CH_2OH$, $R^2 = CO_2Me$, R^3 = H



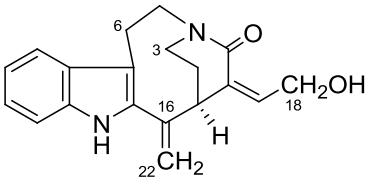
51 R = H
52 $R = CH_2OH$



156



157



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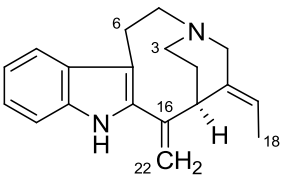
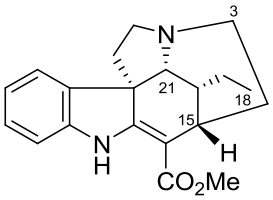
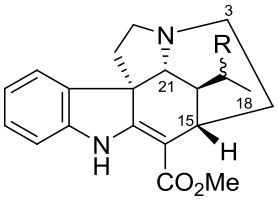


159

160 N(4)→O

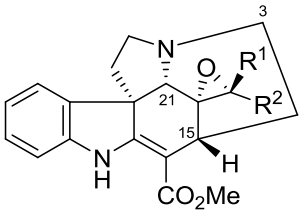


57



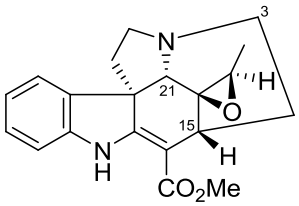
161 R = β-OMe

162 R = α-OMe



163 R^1 = Me, R^2 = H

164 R^1 = H, R^2 = Me



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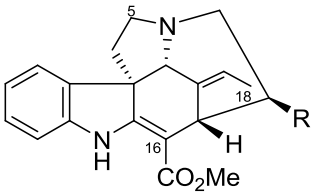
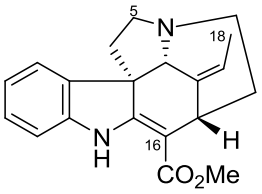


92 R = H

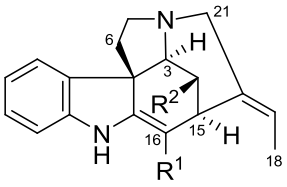
166 R = H, N(4)→O

167 R = OH



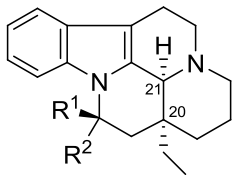
168

169 N(4)→O



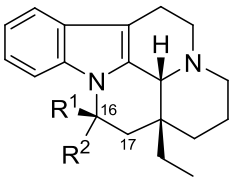
55 R^1 = CHO, R^2 = H

170 R^1 = CO_2Me, R^2 = OH



171 R^1 = H, R^2 = OH

172 R^1 = OH, R^2 = H



29 R^1,R^2 = O

30 R^1 = H, R^2 = nil, $\Delta^{16,17}$

31 R^1 = H, R^2 = OMe

32 R^1 = OMe, R^2 = H

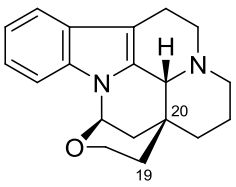
33 R^1 = H, R^2 = OH

34 R^1 = OH, R^2 = H

173 R^1,R^2 = O, N(4)→O

174 R^1 = OEt, R^2 = H

175 R^1 = H, R^2 = OEt



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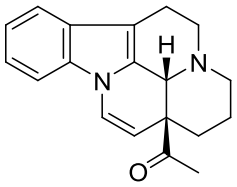

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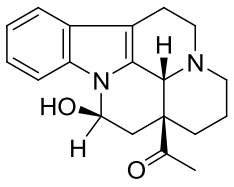
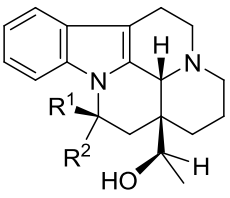
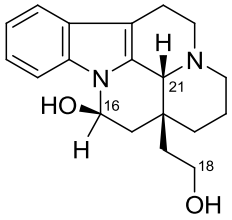


66



67 R^1 = H, R^2 = OH
68 R^1 = OH, R^2 = H



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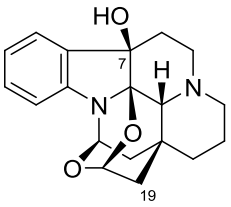

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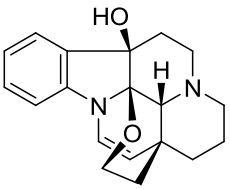

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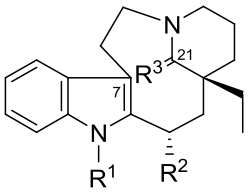
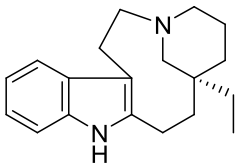


76 R^1 = R^2 = H, R^3 = H,H
180 R^1 = CH_2OCH_3, R^2 = H, R^3 = H,H
181 R^1 = H, R^2 = OH, R^3 = O



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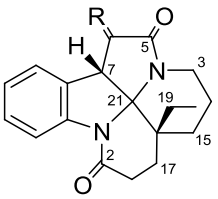
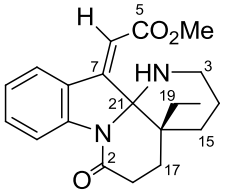


14 R = H,H
15 R = O



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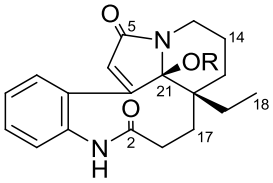
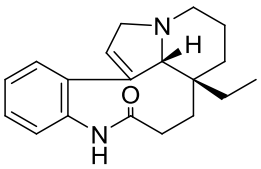
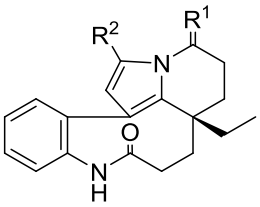


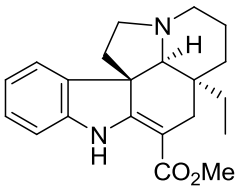
19 R = H
20 R = Me



24



25 R^1 = H,H, R^2 = H
26 R^1 = H,H, R^2 = CHO
27 R^1 = O, R^2 = H
183 R^1 = H,H, R^2 = CH_2OCH_3
184 R^1 = H,H, R^2 = $CH_2OCH_2CH_3$
185 R^1 = H,H, R^2 = CH_2OH



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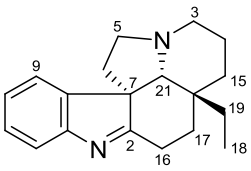

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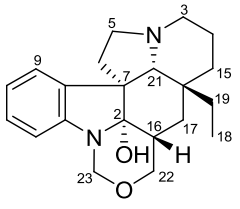

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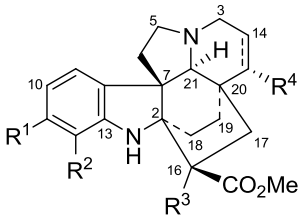
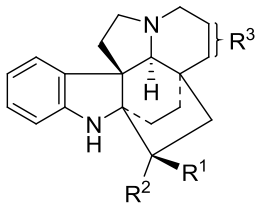
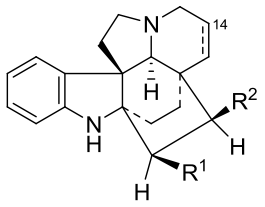


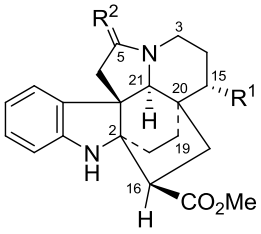
192 R^1,R^2 = OCH_2O, R^3 = OH, R^4 = H, $\Delta^{14,15}$
193 R^1 = R^2 = R^3 = H, R^4 = OMe



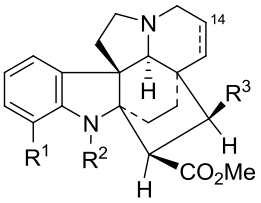
198 R^1 = CO_2H, R^2 = H, R^3 = $\Delta^{14,15}$
199 R^1 = CO_2H, R^2 = H, R^3 = β-epoxide
200 R^1 = H, R^2 = H, R^3 = nil
201 R^1 = CO_2Me, R^2 = H, R^3 = $\Delta^{14,15}$
202 R^1 = CO_2Me, R^2 = H, R^3 = α-epoxide
203 R^1 = CO_2H, R^2 = H, R^3 = nil
204 R^1 = H, R^2 = CO_2Me, R^3 = nil



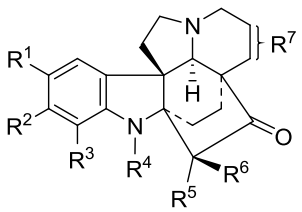
211 R^1 = OH, R^2 = H
212 R^1 = H, R^2 = OH, $\Delta^{14,15}$



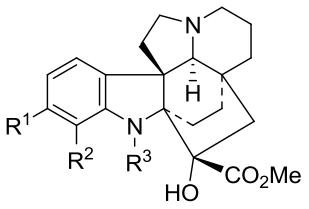
79 R^1 = H, R^2 = H,H
189 R^1 = H, R^2 = H,H, N(4)→O
190 R^1 = OH, R^2 = H,H
191 R^1 = H, R^2 = O



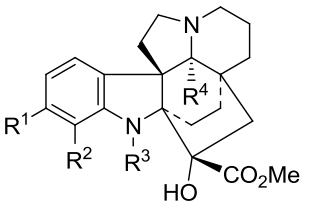
194 R^1 = OMe, R^2 = CO_2Me, R^3 = H
195 R^1 = H, R^2 = CO_2Me, R^3 = OH
196 R^1 = H, R^2 = CO_2Me, R^3 = OH, $\Delta^{14,15}$
197 R^1 = R^3 = H, R^2 = CO_2Me



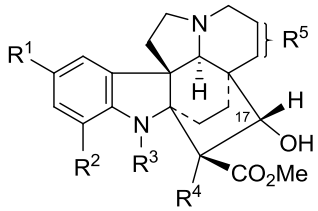
205 R^1 = R^2 = R^3 = R^5 = R^6 = H, R^4 = CO_2Me, R^7 = $\Delta^{14,15}$
206 R^1 = OMe, R^2 = R^3 = R^5 = R^6 = H, R^4 = CO_2Me, R^7 = $\Delta^{14,15}$
207 R^1 = R^2 = R^5 = R^6 = H, R^3 = OMe, R^4 = CO_2Me, R^7 = $\Delta^{14,15}$
208 R^1 = OMe, R^2 = R^3 = R^5 = R^6 = H, R^4 = CO_2Me, R^7 = nil
209 R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H, R^7 = nil
210 R^1 = R^4 = H, R^2,R^3 = OCH_2O, R^5 = OH, R^6 = CO_2Me, R^7 = α-epoxide



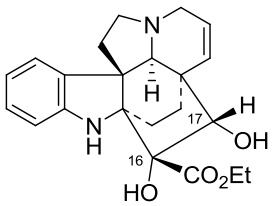
80 R^1,R^2 = OCH_2O, R^3 = CO_2Me
81 R^1,R^2 = OCH_2O, R^3 = H
213 R^1,R^2 = OCH_2O, R^3 = CO_2Me, N(4)→O
214 R^1,R^2 = OCH_2O, R^3 = H, N(4)→O
215 R^1,R^2 = H, R^3 = CO_2Me
216 R^1,R^2 = H, R^3 = CO_2Me, N(4)→O
217 R^1 = OMe, R^2 = OH, R^3 = CO_2Me



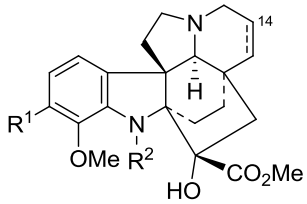
83 R^1,R^2 = OCH_2O, R^3 = CO_2Me, R^4 = OH
224 R^1,R^2 = OCH_2O, R^3 = CO_2Me, R^4 = OH, N→O
225 R^1,R^2 = OCH_2O, R^3 = CO_2Me, R^4 = CN
226 R^1 = R^2 = OMe, R^3 = CO_2Me, R^4 = CN



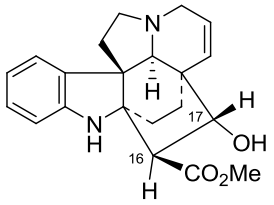
228 R^1 = R^2 = H, R^3 = CO_2Me, R^4 = OH, R^5 = $\Delta^{14,15}$
229 R^1 = R^2 = H, R^3 = CO_2Me, R^4 = OH, R^5 = nil
230 R^1 = R^2 = H, R^3 = CO_2Me, R^4 = OH, R^5 = 15α-OH
231 R^1 = OMe, R^2 = H, R^3 = CO_2Me, R^4 = OH, R^5 = nil
232 R^1 = OMe, R^2 = H, R^3 = CO_2Me, R^4 = OH, R^5 = 15α-OH
233 R^1 = H, R^2 = OMe, R^3 = CO_2Me, R^4 = OH, R^5 = 15α-OH
234 R^1 = R^2 = R^3 = R^4 = H, R^5 = nil
235 R^1 = R^2 = R^3 = H, R^4 = OH, R^5 = $\Delta^{14,15}$
236 R^1 = R^2 = R^3 = H, R^4 = OH, R^5 = nil



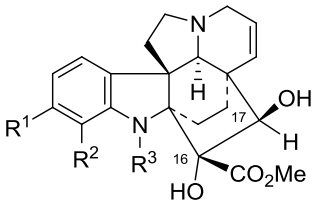
245



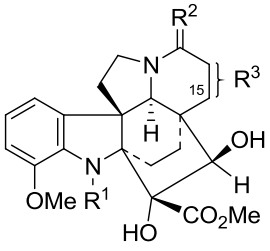
82 R^1 = H, R^2 = CO_2Me
218 R^1 = OMe, R^2 = CO_2Me
219 R^1 = H, R^2 = CO_2Me, N(4)→O
220 R^1 = OMe, R^2 = CO_2Me, N(4)→O
221 R^1 = OH, R^2 = CO_2Me
222 R^1 = R^2 = H
223 R^1 = H, R^2 = CO_2Me, $\Delta^{14,15}$



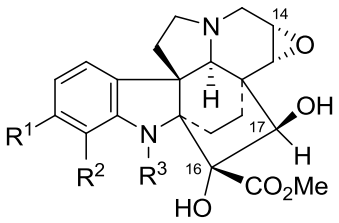
227



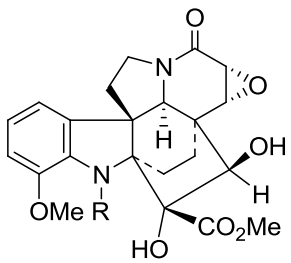
237 R^1 = H, R^2 = OMe, R^3 = CO_2Me
238 R^1 = R^2 = H, R^3 = CO_2Me
239 R^1 = OH, R^2 = OMe, R^3 = CO_2Me
240 R^1 = R^2 = OMe, R^3 = CO_2Me
241 R^1,R^2 = OCH_2O, R^3 = CO_2Me
242 R^1 = R^2 = R^3 = H
243 R^1 = OMe, R^2 = OH, R^3 = H
244 R^1,R^2 = OCH_2O, R^3 =H



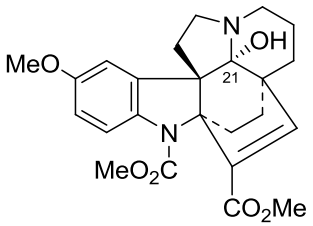
246 R^1 = CO_2Me, R^2 = H,H, R^3 = 15-αOH
247 R^1 = CO_2Me, R^2 = O, R^3 = $\Delta^{14,15}$



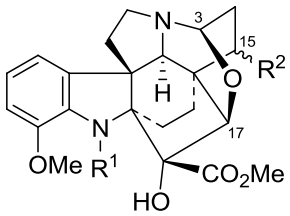
248 R^1,R^2 = OCH_2O, R^3 = CO_2Me
249 R^1 = H, R^2 = OH, R^3 = CO_2Me
250 R^1 = OMe, R^2 = OH, R^3 = CO_2Me
252 R^1 = H, R^2 = OMe, R^3 = CO_2Me



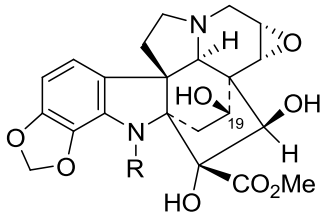
253 R = CO_2Me



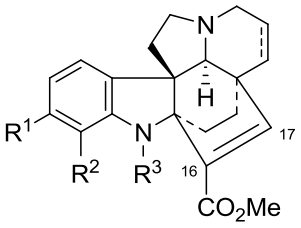
258
259 N→O



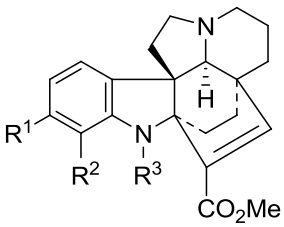
265 R^1 = CO_2Me, R^2 = α-OMe
266 R^1 = CO_2Me, R^2 = α-OEt
267 R^1 = CO_2Me, R^2 = α-OH
268 R^1 = CO_2Me, R^2 = α-OH, N(4)→O
269 R^1 = CO_2Me, R^2 = β-OH



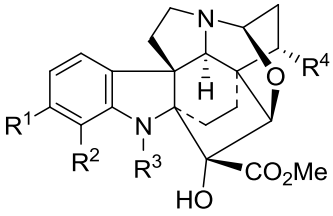
251 R = CO_2Me



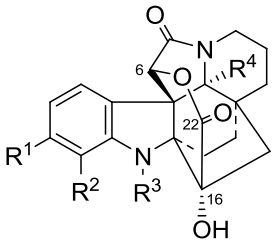
254 R^1 = R^2 = R^3 = H
255 R^1 = R^2 = H, R^3 = CO_2Me
256 R^1,R^2 = OCH_2O, R^3 = H, $\Delta^{14,15}$
257 R^1 = R^3 = H, R^2 = OMe, $\Delta^{14,15}$



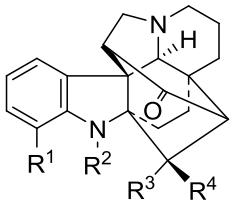
260 R^1,R^2 = OCH_2O, R^3 = CO_2Me
261 R^1 = H, R^2 = OMe, R^3 = CO_2Me
262 R^1 = H, R^2 = OH, R^3 = CO_2Me
263 R^1,R^2 = OCH_2O, R^3 = CO_2Me, N→O
264 R^1 = H, R^2 = OMe, R^3 = CO_2Me, N→O



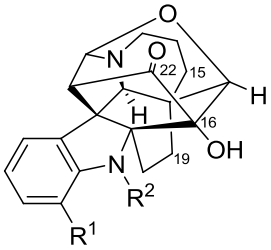
270 R^1 = R^2 = H, R^3 = CO_2Me, R^4 = OH
271 R^1 = R^2 = H, R^3 = CO_2Me, R^4 = OMe
272 R^1,R^2 = OCH_2O, R^3 = CO_2Me, R^4 = OH
273 R^1,R^2 = OCH_2O, R^3 = CO_2Me, R^4 = OMe



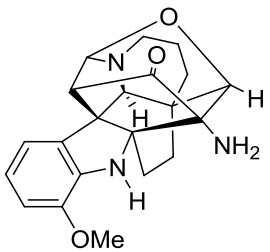
274 R^1, $R^2 = OCH_2O$, $R^3 = CO_2Me$, $R^4 = OH$
275 R^1, $R^2 = OCH_2O$, $R^3 = CO_2Me$, $R^4 = H$
276 $R^1 = R^2 = OMe$, $R^3 = CO_2Me$, $R^4 = H$



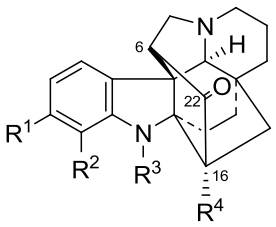
281 $R^1 = R^3 = H$, $R^2 = CO_2Me$, $R^4 = OH$
282 $R^1 = R^4 = H$, $R^2 = CO_2Me$, $R^3 = OH$
283 $R^1 = R^4 = H$, $R^2 = CO_2Me$, $R^3 = OH$, N→O
284 $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = OH$



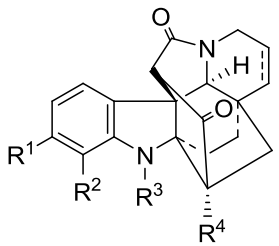
289 $R^1 = OMe$, $R^2 = CO_2Me$, $\Delta^{14,15}$
290 $R^1 = OMe$, $R^2 = H$, $\Delta^{14,15}$
291 $R^1 = OMe$, $R^2 = H$, 15-αOH
292 $R^1 = OMe$, $R^2 = CO_2Me$, 15-αOH
293 $R^1 = H$, $R^2 = CO_2Me$



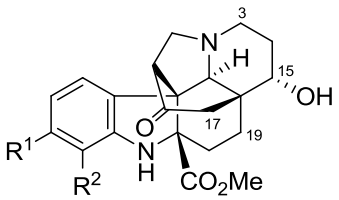
294 $\Delta^{14,15}$
295 15-αOH



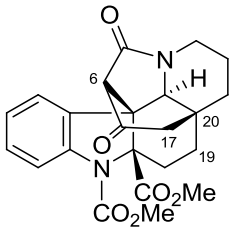
84 $R^1 = R^2 = R^3 = R^4 = H$
85 R^1,$R^2 = OCH_2O$, $R^3 = CO_2Me$, $R^4 = OH$
86 $R^1 = H$, $R^2 = OMe$, $R^3 = CO_2Me$, $R^4 = OH$
277 R^1,$R^2 = OCH_2O$, $R^3 = H$, $R^4 = OH$
278 $R^1 = R^2 = OMe$, $R^3 = CO_2Me$, $R^4 = OH$
279 $R^1 = R^2 = H$, $R^3 = CO_2Me$, $R^4 = OH$
280 $R^1 = R^2 = R^3 = H$, $R^4 = OH$



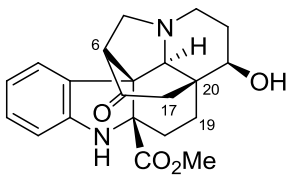
87 R^1,$R^2 = OCH_2O$, $R^3 = CO_2Me$, $R^4 = OH$
88 R^1,$R^2 = OCH_2O$, $R^3 = H$, $R^4 = OH$
285 $R^1 = R^2 = OMe$, $R^3 = CO_2Me$, $R^4 = OH$
286 $R^1 = R^2 = R^3 = R^4 = H$, $\Delta^{14,15}$
287 $R^1 = R^2 = R^3 = R^4 = H$
288 $R^1 = R^2 = R^4 = H$, $R^3 = CO_2Me$



299 $R^1 = R^2 = H$
300 R^1,$R^2 = OCH_2O$
301 $R^1 = H$, $R^2 = OMe$



302



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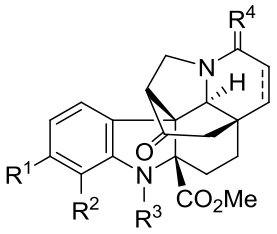
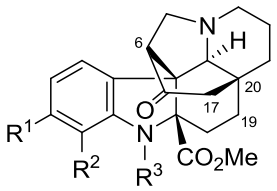
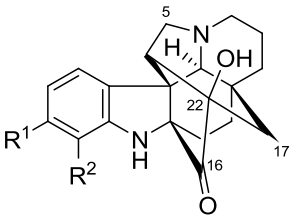


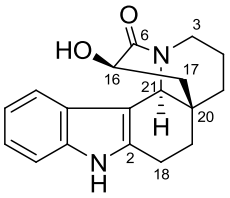
296 R^1 = H, R^2 = OMe, R^3 = CO_2Me, R^4 = O
297 R^1 = R^2 = OMe, R^3 = CO_2Me, R^4 = H,H, $\Delta^{14,15}$
298 R^1 = R^3 = H, R^2 = OMe, R^4 = H,H, $\Delta^{14,15}$
307 R^1 = R^2 = OMe, R^3 = H, R^4 = O, $\Delta^{14,15}$
308 R^1,R^2 = OCH_2O, R^3 = H, R^4 = H,H, $\Delta^{14,15}$
309 R^1 = R^2 = R^3 = H, R^4 = H,H, $\Delta^{14,15}$
310 R^1 = R^2 = R^3 = H, R^4 = O, $\Delta^{14,15}$
311 R^1,R^2 = OCH_2O, R^3 = H, R^4 = O, $\Delta^{14,15}$
312 R^1 = R^3 = H, R^2 = OMe, R^4 = O, $\Delta^{14,15}$



95 R^1,R^2 = OCH_2O, R^3 = H
96 R^1,R^2 = OCH_2O, R^3 = CO_2Me
97 R^1 = R^2 = H, R^3 = CO_2Me
98 R^1 = R^2 = R^3 = H
99 R^1 = H, R^2 = OMe, R^3 = CO_2Me
304 R^1 = H, R^2 = OH, R^3 = H
305 R^1 = R^2 = OMe, R^3 = CO_2Me
306 R^1 = R^3 = H, R^2 = OMe



313 R^1,R^2 = OCH_2O
314 R^1 = R^2 = H



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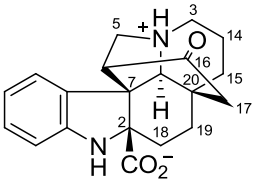

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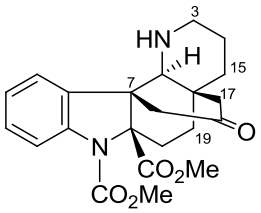

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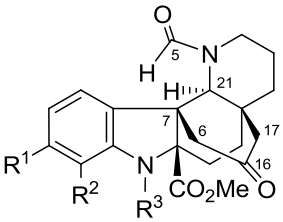
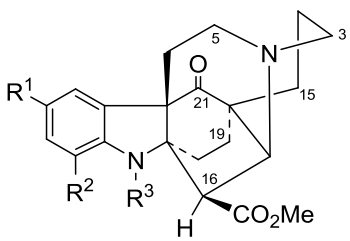
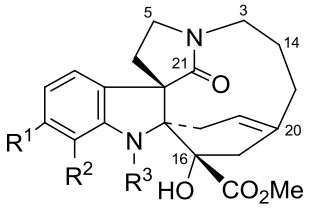


318 R^1,R^2 = OCH_2O, R^3 = CO_2Me
319 R^1 = R^2 = H, R^3 = CO_2Me
320 R^1 = R^2 = R^3 = H

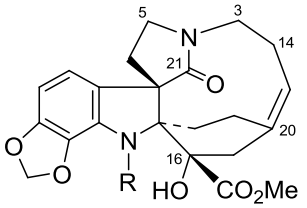


321 R^1 = OMe, R^2 = H, R^3 = CO_2Me
322 R^1 = H, R^2 = OMe, R^3 = CO_2Me
323 R^1 = R^2 = H, R^3 = CO_2Me

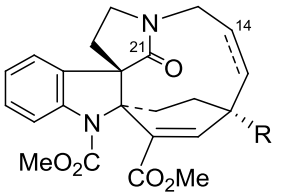


324 R^1,R^2 = OCH_2O, R^3 = CO_2Me

325 R^1 = R^2 = OMe, R^3 = CO_2Me



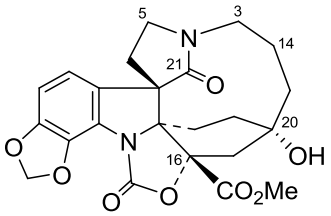
326 R = CO_2Me



327 R = OH

328 R = H

329 R = OH, $\Delta^{14,15}$



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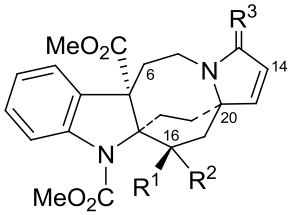
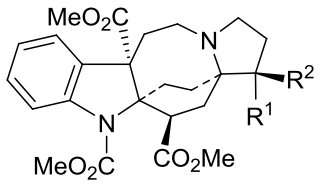


332 R^1 = H, R^2 = CO_2Me, R^3 = O

334 R^1 = H, R^2 = CO_2Me, R^3 = H,H

335 R^1 = CO_2Me, R^2 = H, R^3 = H,H

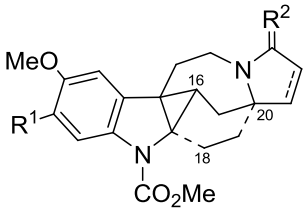
336 R^1 = CO_2Me, R^2 = H, R^3 = O



331 R^1 = H, R^2 = H

337 R^1 = OH, R^2 = H

338 R^1 = H, R^2 = OH

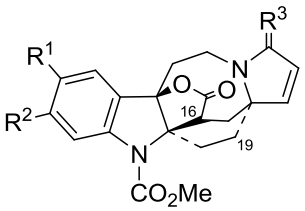


339 R^1 = H, R^2 = O, $\Delta^{14,15}$

340 R^1 = H, R^2 = H,H, $\Delta^{14,15}$

341 R^1 = H, R^2 = H,H

342 R^1 = OMe, R^2 = H,H, $\Delta^{14,15}$



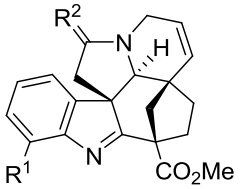
333 R^1 = R^2 = H, R^3 = O

343 R^1 = R^2 = H, R^3 = H,H

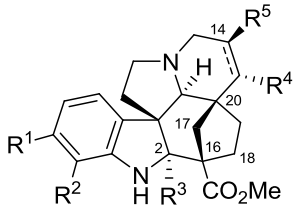
344 R^1 = OMe, R^2 = H, R^3 = H,H

345 R^1 = OMe, R^2 = OMe, R^3 = H,H

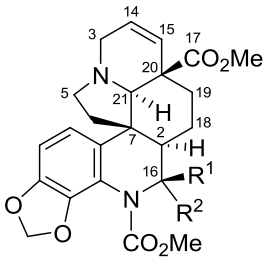
346 R^1 = OMe, R^2 = H, R^3 = O



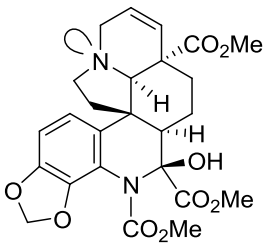
347 R^1 = OMe, R^2 = O
351 R^1 = H, R^2 = H,H
352 R^1 = OMe, R^2 = H,H



348 R^1 = R^4 = R^5 = H, R^2 = OMe, R^3 = OH, $\Delta^{14,15}$
349 R^1 = R^5 = H, R^2 = OMe, R^3 = R^4 = OH
350 R^1 = H, R^2 = OMe, R^3 = R^4 = R^5 = OH
353 R^1 = OMe, R^2 = R^3 = R^4 = R^5 = H



354 R^1 = CO_2Me, R^2 = OH
355 R^1 = OH, R^2 = CO_2Me



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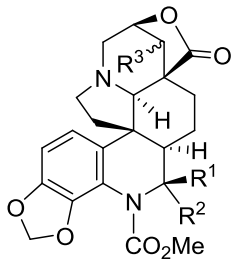
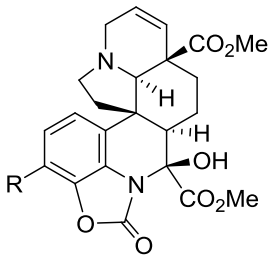
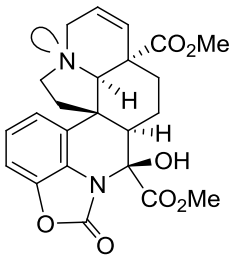


357 R^1 = OH, R^2 = CO_2Me, R^3 = α-OH
358 R^1 = CO_2Me, R^2 = OH, R^3 = α-OH
359 R^1 = OH, R^2 = CO_2Me, R^3 = β-OH



360 R = H
361 R = OMe



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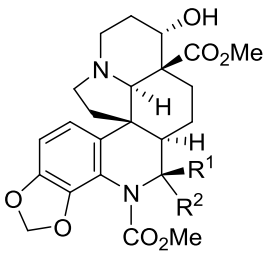
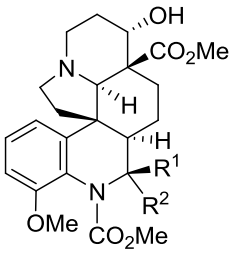
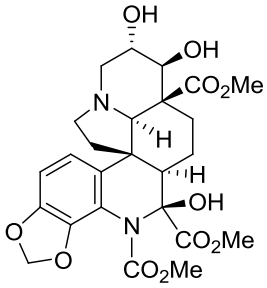


363 R^1 = CO_2Me, R^2 = OH
364 R^1 = OH, R^2 = CO_2Me



365 R^1 = CO_2Me, R^2 = OH
366 R^1 = OH, R^2 = CO_2Me



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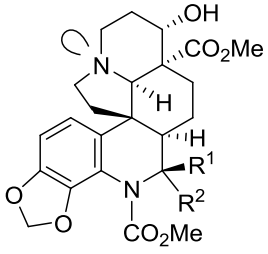
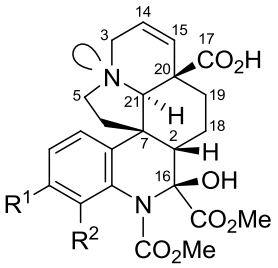
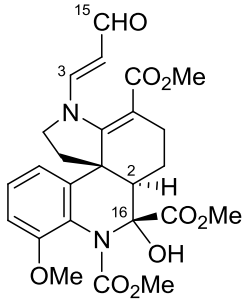


368 R^1 = CO_2Me, R^2 = OH
369 R^1 = OH, R^2 = CO_2Me



370 R^1,R^2 = OCH_2O

371 R^1 = H, R^2 = OMe



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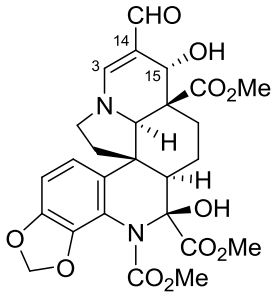

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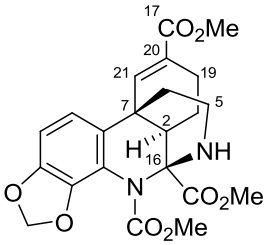

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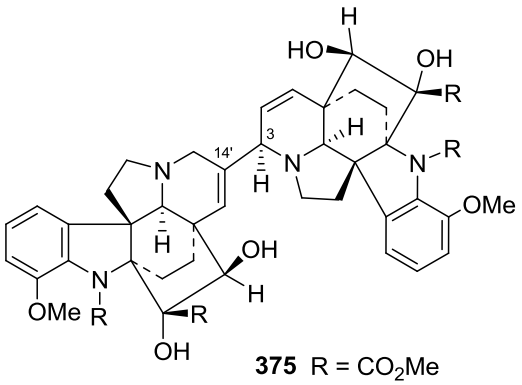
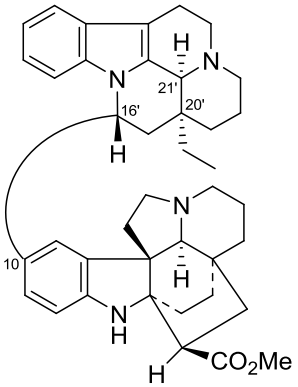


375 R = CO_2Me



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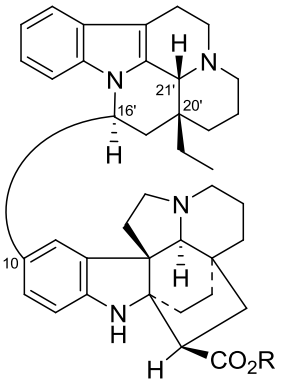
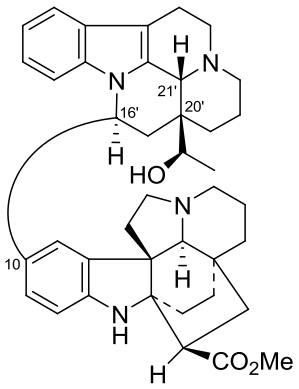


100 R = Me

377 R = H



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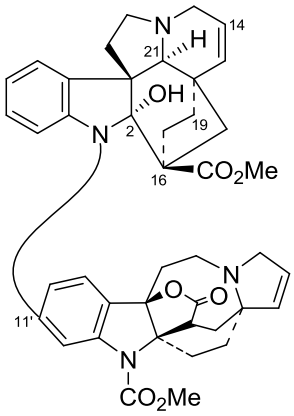

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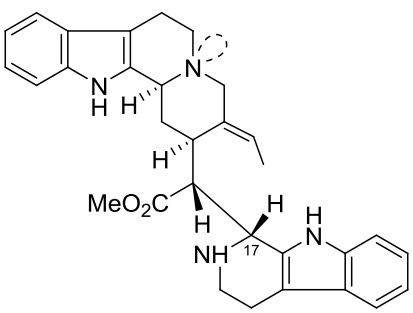

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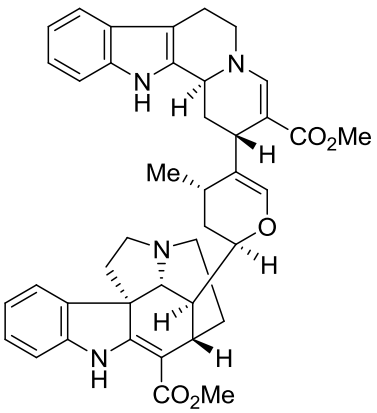


381

1.6 Fungi

1.6.1 The Genus *Penicillium*

Penicillium belongs to the family Trichocomaceae of the order Eurotiales of the kingdom Fungi.[262,263] The genus is characterized by the production of asexual spores (conidia) from verticels of phialides supported on a conidiophore.[262] The conidiophore lacks a distinctive foot-cell, and it branches at the apex into a brush-like structure known as the penicillus.[263] The taxonomy of this genus is complicated as its classification is based mainly on the structures of the conidiophore and conidia.[264] A total of 225 species and 347 synonyms are recognized by Pitt *et. al.* and the number increases every year.[265]

1.6.2 Chemical Constituents of the Genus *Penicillium*

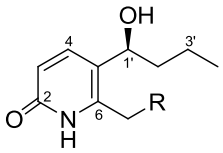
Penicillium species are known to produce a great variety of compounds including, β-lactam antibiotics, alkaloids (*e.g*, indole, quinoline, ergot, *etc*.), diketopiperazines, and polyketides.[266] However, the production of secondary metabolites from a species may vary and is highly dependent on some variables, such as the medium ingredients, types of Petri dishes, volume of media, method of inoculation, and incubation conditions including temperature, air exchange, duration, and sporadic exposure to light.[265] Several compounds of different structural classes isolated from this genus are given in Table 1.3.

Table 1.3: Selected Compounds of Different Structural Classes from *Penicillium*

Fungi	Chemical Constituents	Structural Class	References
P. aurantiogriseum (Sponge-derived fungus)	Aurantiomide A (**391**)	Quinazoline alkaloids	267
	Aurantiomide B (**392**)		267
	Aurantiomide C (**393**)		267
P. chrysogenum	Chrysogedone A (**382**)	2-Pyridone alkaloids	268
	Chrysogedone B (**383**)		268
	Chrysogeside A (**416**)	Cerebroside alkaloids	268
	Chrysogeside B (**417**)		268
	Chrysogeside C (**418**)		268
	Chrysogeside D (**419**)		268
	Chrysogeside E (**420**)		268
	Penicillin G (**396**)	β-lactam antibiotic	269
P. chrysogenum (Sponge-derived fungus)	Sorbicillactone A (**397**)	Sorbicillinoid alkaloids	270
	Sorbicillactone B (**398**)		270
	Sorbivinetone (**421**)		270
P. citrinum	Agroclavine I (**395**)	Ergot alkaloid	271
	Quinocitrinin A (**390**)	Quinoline alkaloid	272
P. citrinum (Marine-derived fungus)	Scalusamide A (**413**)	Pyrrolidine alkaloids	273
	Scalusamide B (**414**)		273
	Scalusamide C (**415**)		273
P. citrinum (Sponge-derived fungus)	22-Acetylisocyclocitrinol A (**423**)	Steroids	274
	Isocyclocitrinol A (**424**)		274
P. cluniae	Paraherquamide H (**403**)	Oxindole alkaloids	275
	Paraherquamide I (**404**)		275
P. crustosum Thom	Thomitrem A (**405**)	Indole alkaloids	276
	Thomitrem E (**406**)		276
P. decaturense	Decaturin A (**401**)	Oxalicine alkaloids	277
	15-Deoxyoxalicine B (**400**)		277
P. fellutanum	Fellutanine A (**407**)	Indole-containing diketopiperazine alkaloids	278
	Fellutanine B (**408**)		278
	Fellutanine C (**409**)		278
	Fellutanine D (**410**)		278

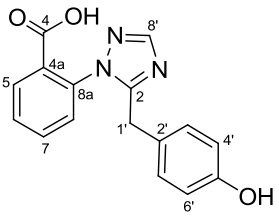
Table 1.3, continued

Fungi	Chemical Constituents	Structural Class	References
P. griseofulvum (Ocean sediment derived fungus)	Variecolorin M (**387**)	Indole-containing diketopiperazine alkaloids	279
	Variecolorin N (**388**)		279
	Variecolorin O (**389**)		279
P. janczewskii Zalessky (Marine-derived fungus)	3*S**,4*R**-dihydroxy-4-(4′-methoxyphenyl)-3,4-dihydro-2(1*H*)-quinolinone (**385**)	Quinolinone alkaloids	280
	3*R**,4*R**-dihydroxy-4-(4′-methoxyphenyl)-3,4-dihydro-2(1*H*)-quinolinone (**386**)		280
P. paneum (Marine-derived fungus)	Penipanoid A (**384**)	Triazole alkaloid	281
P. rivulum Frisvad	Communesin G (**411**)	Alkaloids	282
	Communesin H (**412**)		282
P. roqueforti	Roquefortine D (**399**)	Indole alkaloid	283,284
P. solitum	Solistatin (**422**)	Statin (analogue of compactin)	285
P. thiersii	Decaturin B (**402**)	Oxalicine alkaloid	277
P. verrucosum	Verrucine F (**394**)	Quinazoline alkaloid	286



382 R = H

383 R = OH



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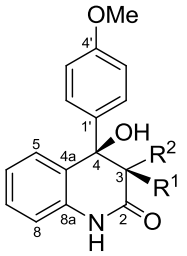
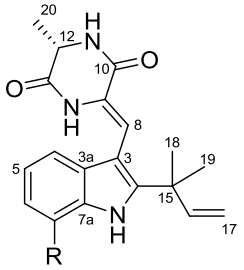
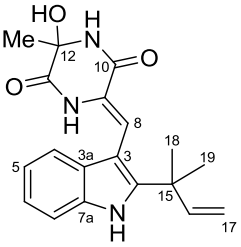


385 R^1 = H, R^2 = OH

386 R^1 = OH, R^2 = H





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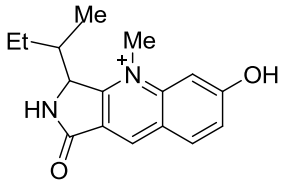

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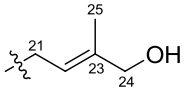
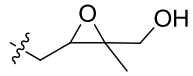
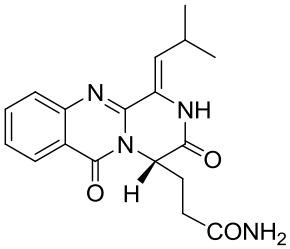
387 R =



388 R =





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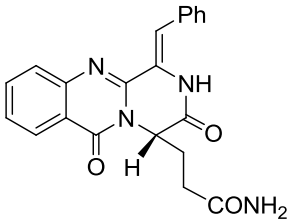

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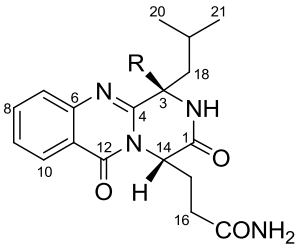
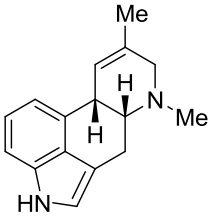


391 R = OMe

392 R = OH



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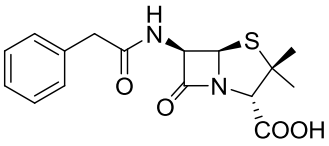

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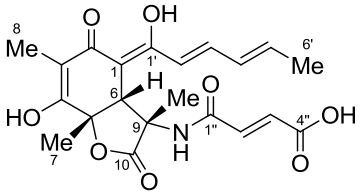

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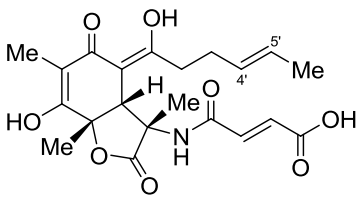

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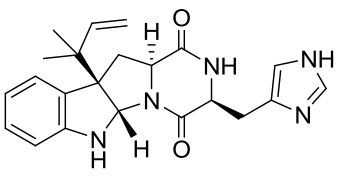

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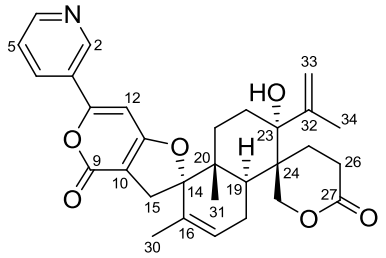

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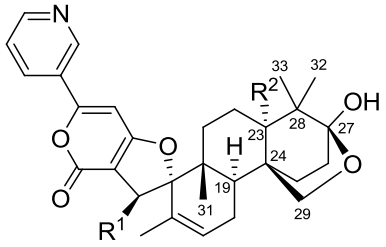
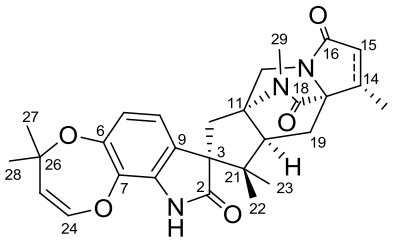


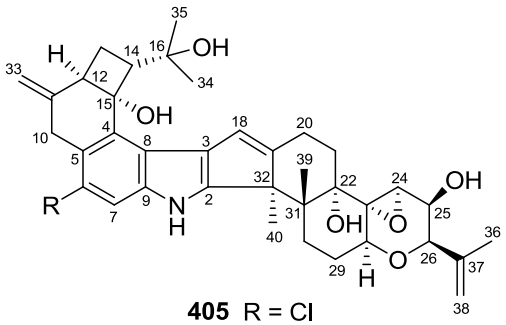
401 R^1 = H, R^2 = OH

402 R^1 = OH, R^2 = H



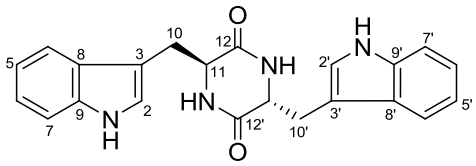
403

404 $\Delta^{14,15}$



405 R = Cl

406 R = H



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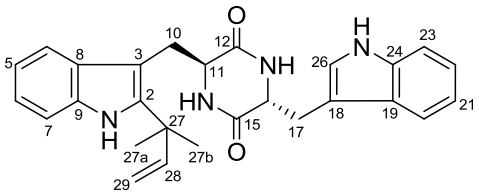

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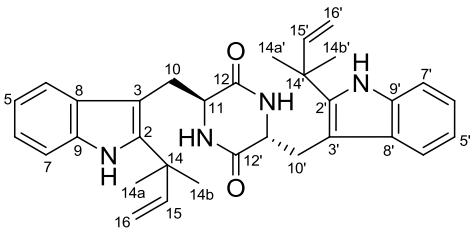

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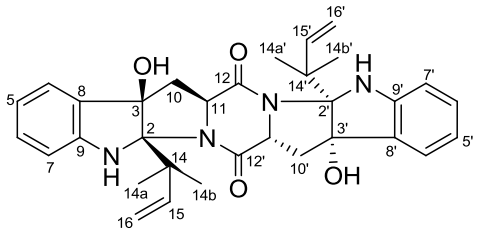

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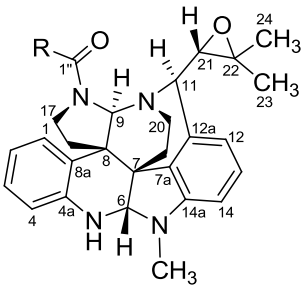
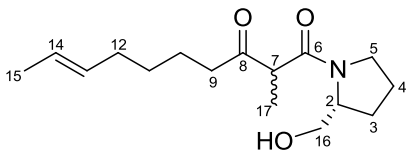


411 R = CH_2CH_3

412 R = $CH_2CH_2CH_3$



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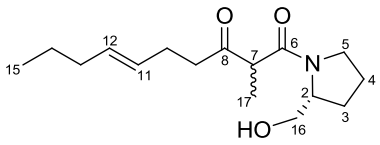

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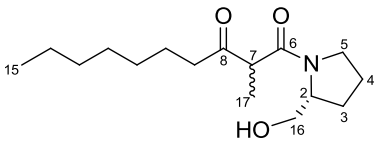

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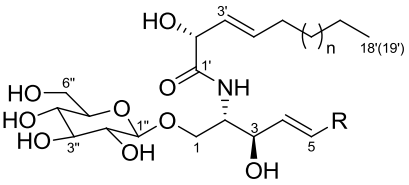
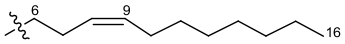
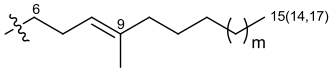


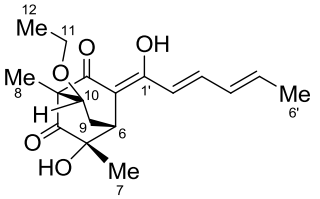
416 n = 11, R =



417–419 n = 12, R =



417 m = 2; **418** m = 1; **419** m = 4



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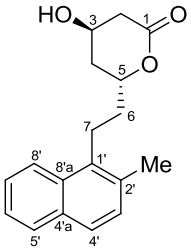

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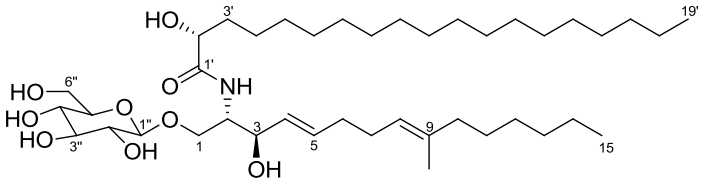

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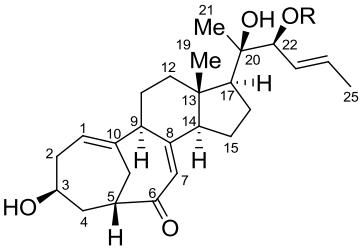


423 R = $COCH_3$

424 R = H

1.7 Bacteria

1.7.1 The Genus *Streptomyces*

Streptomyces belongs to the family Streptomycetaceae of the order Actinomycetales of the kingdom Bacteria. This genus produces a well-developed mycelium and the hyphae vary greatly in length. The vegetative mycelium does not form cross walls and it does not break up into rod-shaped and coccus-like bodies. The spores or conidia are formed in special spore-bearing hyphae or sporophores which arise from the aerial mycelium, either monopodially or in the form of tufts or whorls.[287] To date, a total of 576 species are reported and the number of new species increases every year.[288]

1.7.2 Chemical Constituents of the Genus *Streptomyces*

Streptomyces species also produce secondary metabolites of different structural classes. Some examples are given in Table 1.4.

Table 1.4: Selected Compounds of Different Structural Classes from *Streptomyces*

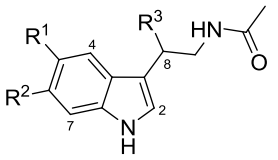
Bacteria	Chemical Constituents	Structural Class	References
S. anulatus	Telomestatin (**461**)	Macrocyclic alkaloid	289
S. fumanus	Dioxapyrrolomycin (**436**)	Pyrrole alkaloids	290
	Pyrrolomycin G (**437**)		290
	Pyrrolomycin H (**438**)		290
	Pyrrolomycin I (**439**)		290
	Pyrrolomycin J (**440**)		290

Table 1.4, continued

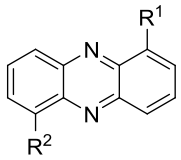
Bacteria	Chemical Constituents	Structural Class	References
S. griseus	Cephamycin A (**445**)	β-lactam antibiotic	291
	Cephamycin B (**446**)		291
	Farinamycin (**447**)	Quinazoline	292
	Streptomycin (**458**)	Aminoglycoside	293,294
S. hygroscopicus	4,5-Dihydro-19-*S*-methylgeldanamycin (**459**)	Benzoquinone	295
	19-*S*-Methylgeldanamycin (**460**)	Ansamycin	295
S. hygroscopicus	Mannopeptimycin α (**462**)	Glycopeptides	296
	Mannopeptimycin β (**463**)		296
	Mannopeptimycin γ (**464**)		296
	Mannopeptimycin δ (**465**)		296
	Mannopeptimycin ∈ (**466**)		296
S. longisporus	Metacycloprodigiosin (**444**)	Tripyrrole alkaloid	297
S. nitrosporeus	Benzastatin E (**448**)	Indoline alkaloids	298
	Benzastatin F (**449**)		298
	Benzastatin G (**450**)		298
S. platensis	Platencin A_1 (**441**)	Platensimycins	299
	Platensimycin (**442**)		299
	Platensimide A (**443**)	Platencin	299
S. staurosporeus	N_b-Acetyltryptamine-5-*O*-β-$_D$-quinovopyranoside (**425**)	Serotonins	300
	N_b-Acetyltryptamine-5-*O*-α-L-rhamnopyranoside (**426**)		300
	5-Fluoro-β-hydroxy-N_b-acetyltryptamine (**427**)		300
	6-Fluoro-β-hydroxy-N_b-acetyltryptamine (**428**)		300
	β-Hydroxy-N_b-acetyltryptamine (**429**)		300
S. thioluteus	3-Anisylidene-6-benzylidene-2,5-dioxopiperazine (**435**)	Dioxopiperazine	301
	2-Ethanolamino-3H-phenoxazin-3-one (**434**)	Phenoxazinone	301
	1,6-Dimethoxyphenazine (**430**)	Phenazines	301
	6-Methoxy-1-phenazinol (**431**)		301
	1,6-Phenazinediol (**432**)		301
	1-Phenazinol (**433**)		301

Table 1.4, continued

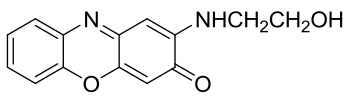
Bacteria	Chemical Constituents	Structural Class	References
S. uncialis	Cladoniamide A (**451**)	Tryptophan-derived	302
	Cladoniamide B (**452**)	alkaloids	302
	Cladoniamide C (**453**)		302
	Cladoniamide D (**454**)		302
	Cladoniamide E (**455**)		302
	Cladoniamide F (**456**)		302
	Cladoniamide G (**457**)		302



425 R^1 = *O*-β-$_D$-quinovose, R^2 = R^3 = H
426 R^1 = *O*-α-$_L$-rhamnose, R^2 = R^3 = H
427 R^1 = F, R^2 = H, R^3 = OH
428 R^1 = H, R^2 = F, R^3 = OH
429 R^1 = R^2 = H, R^3 = OH



430 R^1 = R^2 = OCH_3
431 R^1 = OCH_3, R^2 = OH
432 R^1 = R^2 = OH
433 R^1 = OH, R^2 = H



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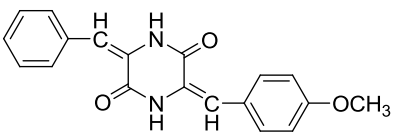

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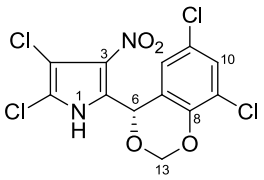

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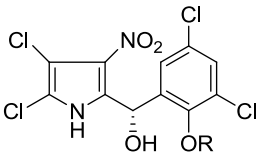
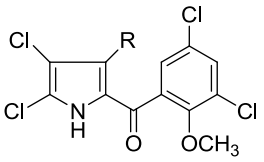
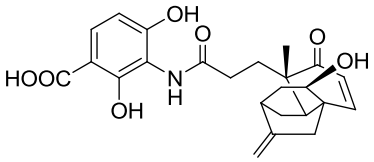


437 R = H
438 R = CH_3



439 R = H
440 R = Cl



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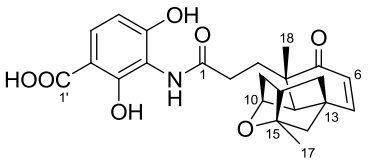

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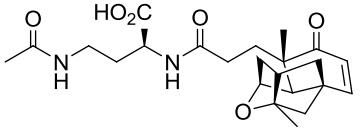

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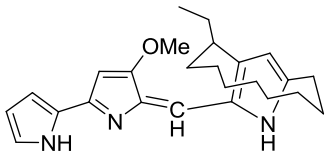

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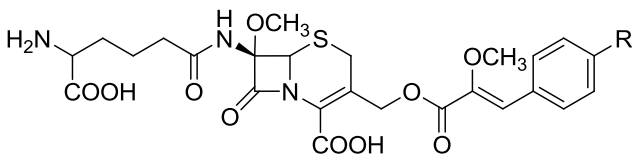
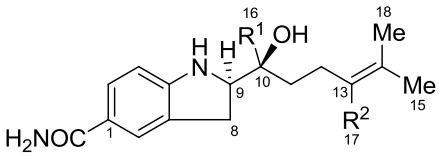
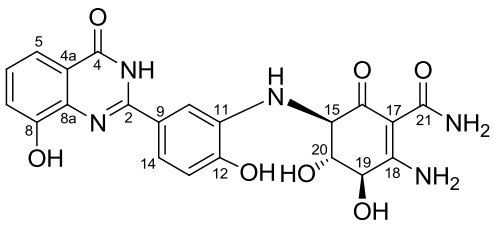


445 R = OSO_2OH
446 R = OH



448 R^1 = CH_2OMe, R^2 = Me
449 R^1 = R^2 = Me
450 R^1 = Me, R^2 = H



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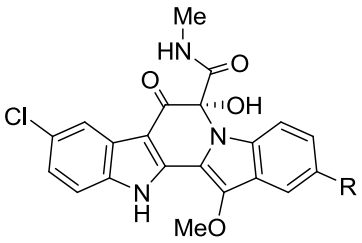
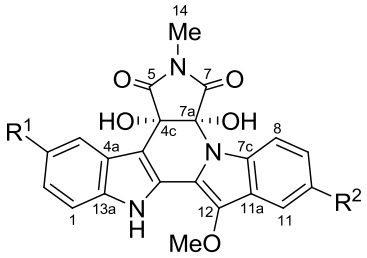
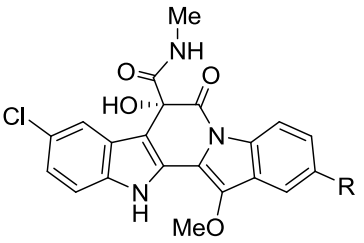


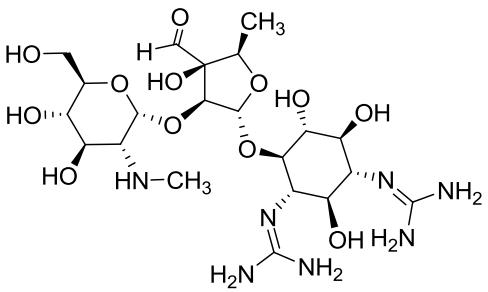
454 R = H
455 R = Cl



451 R^1 = Cl, R^2 = H
452 R^1 = R^2 = Cl
453 R^1 = R^2 = H



456 R = H
457 R = Cl



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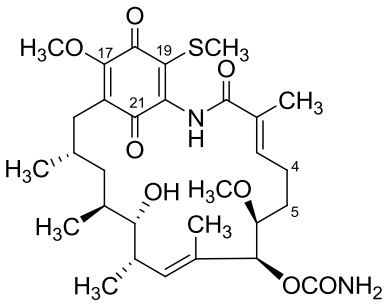

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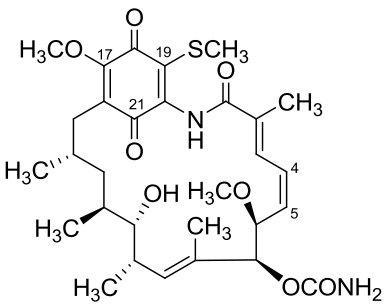

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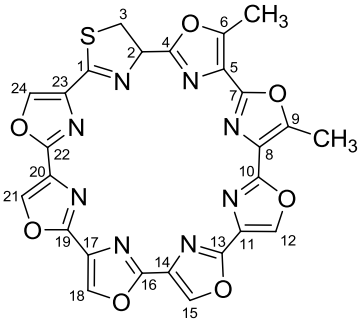

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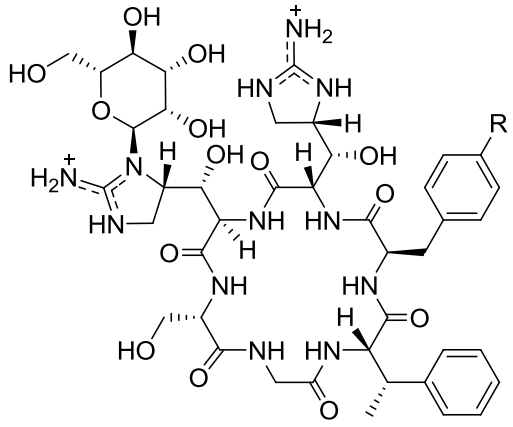
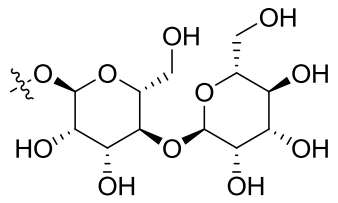
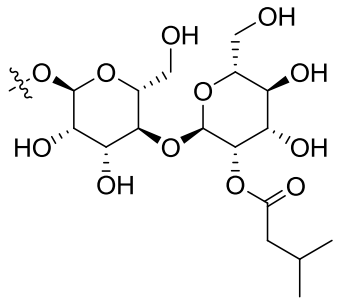


462 R =

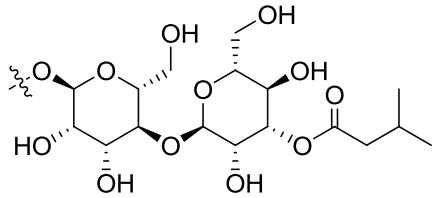


463 R = OH

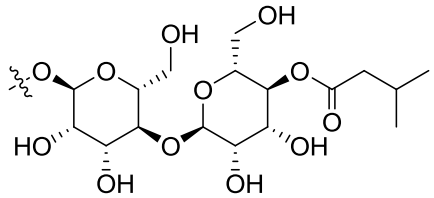
464 R =



465 R =



466 R =



1.8 Objective of the Present Research

The aim of the present research is to carry out a detailed investigation of the alkaloid composition of *Leuconotis griffithii* (collected from Pahang, Peninsular Malaysia) and *Kopsia pauciflora* (collected from Terengganu, Peninsular Malaysia) involving the characterization of the isolated alkaloids, the discovery of new alkaloid structures, and the screening and evaluation of biological activity. In addition, several *Penicillium* and *Streptomyces* strains were selected and screened for their chemical constituents with emphasis on the discovery of new natural products.

Chapter Two

2 Results and Discussion

2.1 Alkaloids from *Leuconotis griffithii*

Investigation of the alkaloidal content of the Malayan *Leuconotis griffithii* has provided a total of 60 alkaloids, of which 24 are new. Of these, several such as the tetracyclic ring-opened oxindole leucolusine (**1**), the strychnan alkaloids, leuconicines A–G (**2**–**8**), the ring-C contracted rhazinilam alkaloid, *nor*-rhazinicine (**22**), the unprecedented eburnane–quinoline dimer, leucophyllidine (**36**), the eburnane–sarpagine bisindole, leuconoline (**37**), the aspidospermatan–aspidospermatan bisindole, leucofoline (**38**) and the *Strychnos*–*Strychnos* bisindoles, leucoridines A–D (**39**–**42**), are notable for incorporating novel or intriguing molecular skeletons. The remaining new alkaloids isolated include the leuconoxine–leuconolam–rhazinilam alkaloids, leuconodines A–E (**9**–**13**), 3,14-dehydroleuconolam (**18**), and 5,21-dihydrorhazinilam *N*-oxide (**23**), and the eburnane alkaloid, (–)-eburnamaline (**28**). 5,21-Dihydrorhazinilam *N*-oxide (**23**), leucophyllidine (**36**), and leucoridine A (**39**) showed pronounced cytotoxic effects against human KB cells, while leuconicines A–B (**2**–**3**) showed strong ability to reverse multi-drug resistant in vincristine-resistant KB (VJ300) cells. The alkaloid composition of the stem-bark of *L. griffithii* is summarized in Table 2.1.

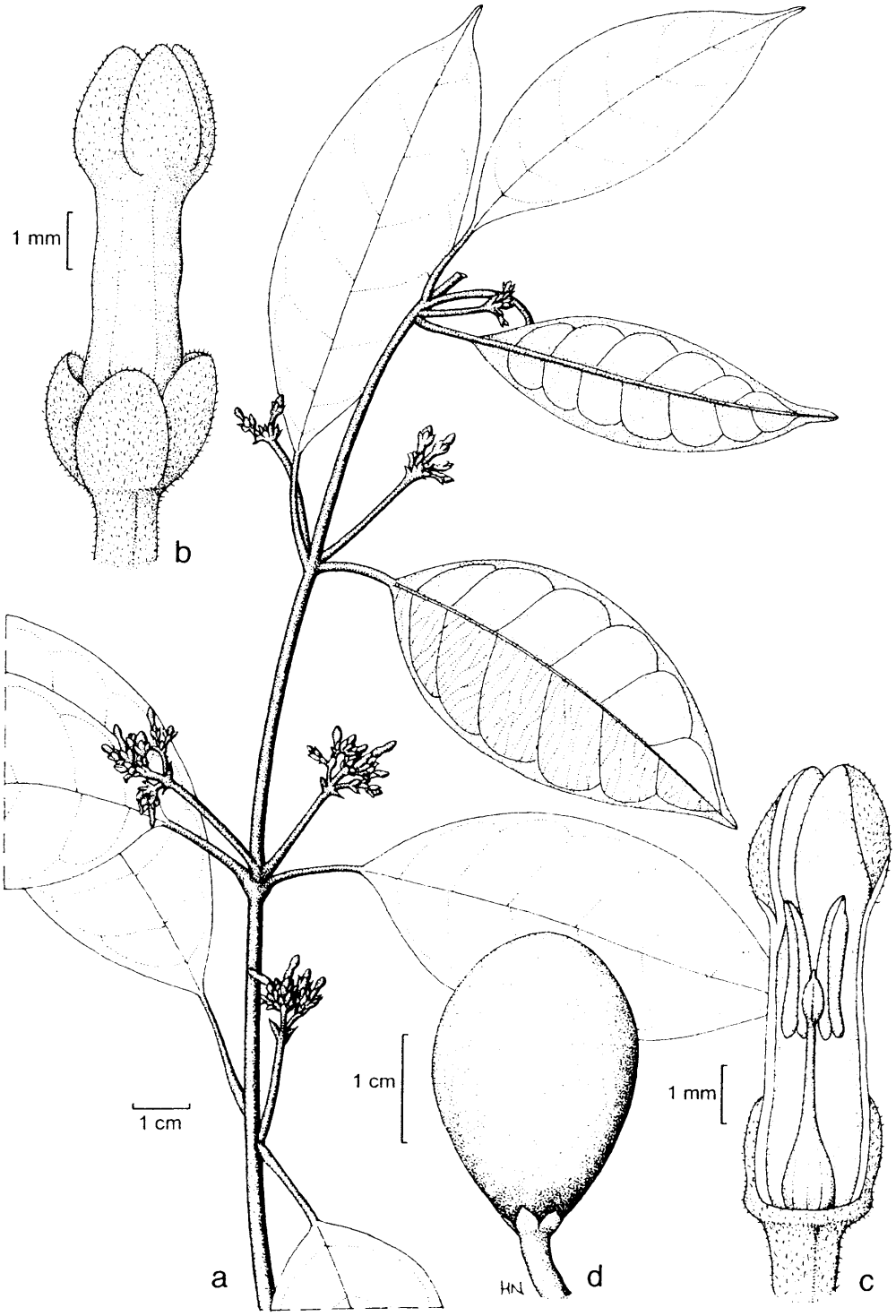
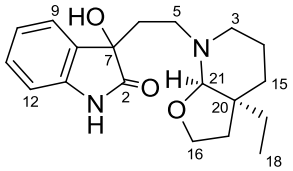


Figure 2.1: *L. griffithii* Hook. f. a. habit; b. flower; c.dissected flower; d. fruit



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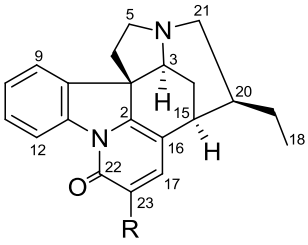
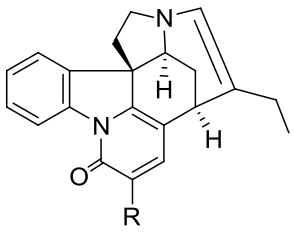
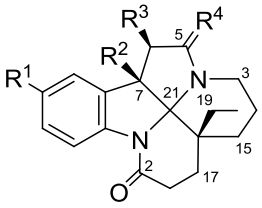


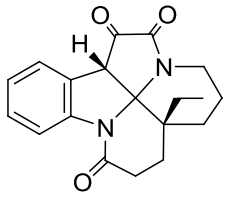
2 R = $CONH_2$
3 R = CO_2Me
7 R = $CONH_2$, N(4)→O
8 R = CO_2Me, N(4)→O



4 R = $CONH_2$
5 R = CO_2Me
6 R = COOH



9 $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = O$
10 $R^1 = R^3 = H$, R^2 = OH, $R^4 = O$
11 $R^1 = OH$, $R^2 = R^3 = H$, $R^4 = O$
12 $R^1 = R^2 = R^3 = H$, $R^4 = H,H$
13 $R^1 = R^3 = H$, $R^2 = OH$, $R^4 = H,H$
14 $R^1 = R^2 = R^3 = H$, $R^4 = O$



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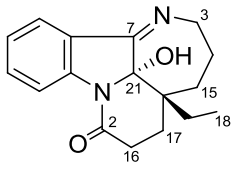

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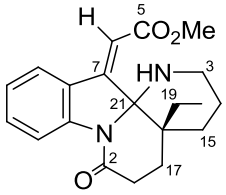

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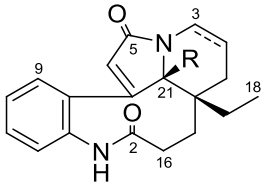
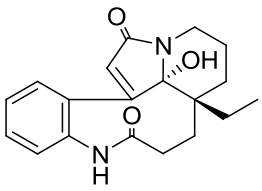


18 R = OH, $\Delta^{3,14}$
19 R = OH
20 R = OMe



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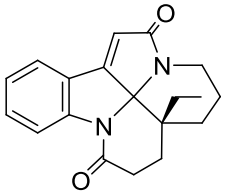
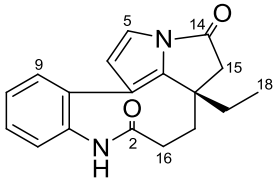


21a



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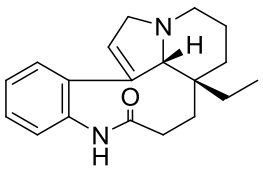
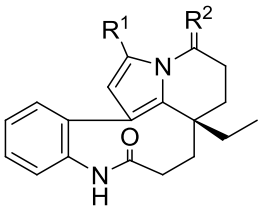
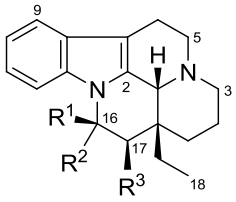


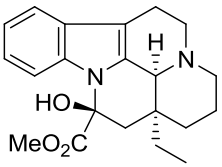
23 N(4)→O
24



25 $R^1 = H$, $R^2 = H,H$
26 $R^1 = CHO$, $R^2 = H,H$
27 $R^1 = H$, $R^2 = O$



28 $R^1 = R^3 = OH$, $R^2 = H$
29 $R^1, R^2 = O$, $R^3 = H$
30 $R^1 = R^3 = H$, R^2 = nil $\Delta^{16,17}$
31 $R^1 = R^3 = H$, $R^2 = OMe$
32 $R^1 = OMe$, $R^2 = R^3 = H$
33 $R^1 = R^3 = H$, $R^2 = OH$
34 $R^1 = OH$, $R^2 = R^3 = H$



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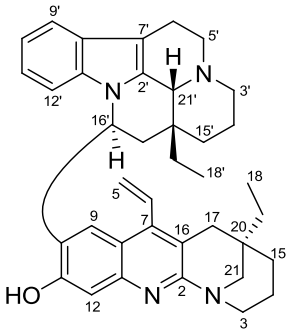

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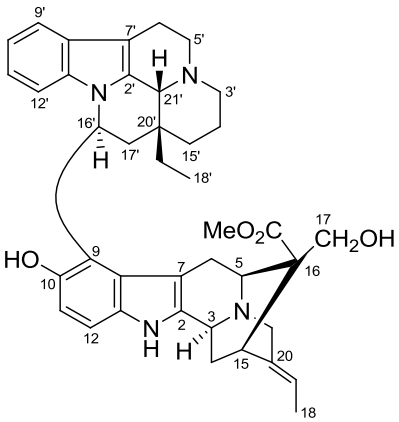

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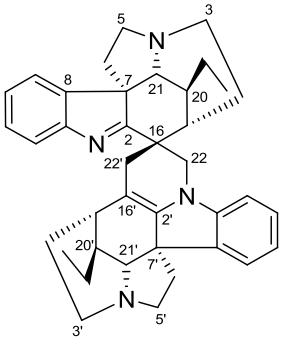

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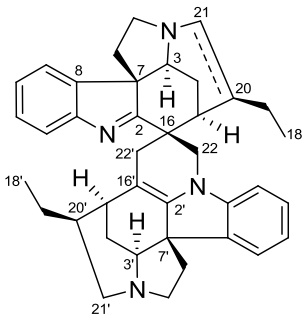
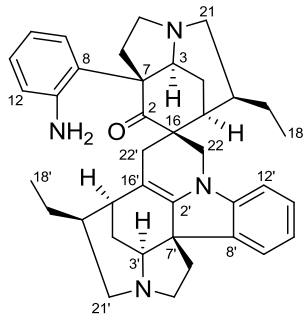


39
40 $\Delta^{20,21}$



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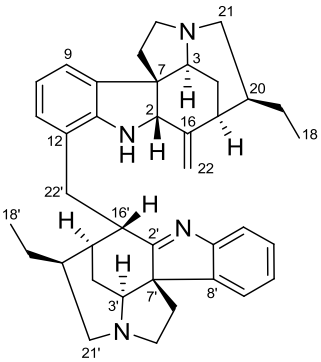

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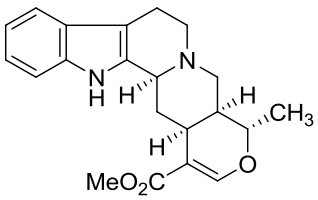

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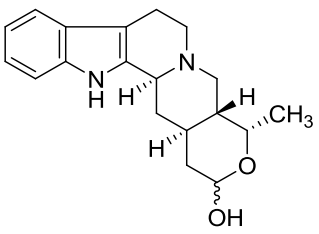
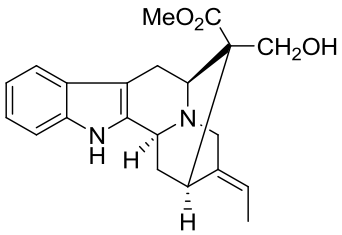


44 17*S*
45 17*R*



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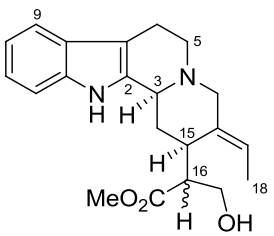
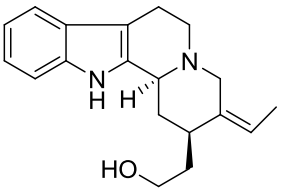


47 16*R*
48 16*S*



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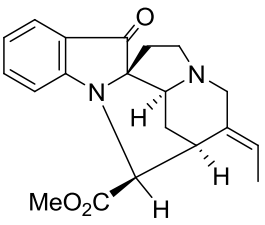

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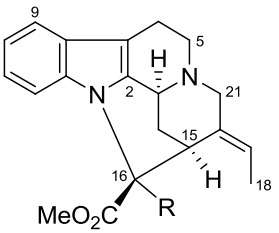
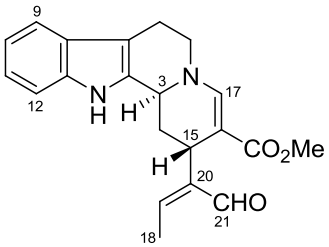


51 R = H
52 R = CH_2OH



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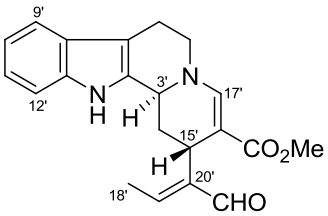

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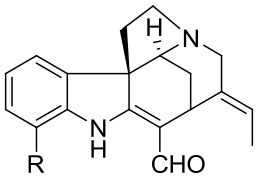
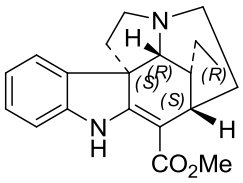
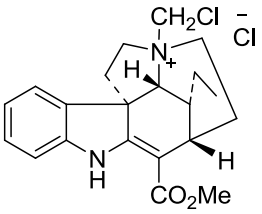


55 R = H
56 R = OH



57
58 N(4)→O



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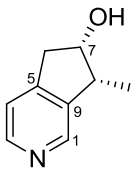

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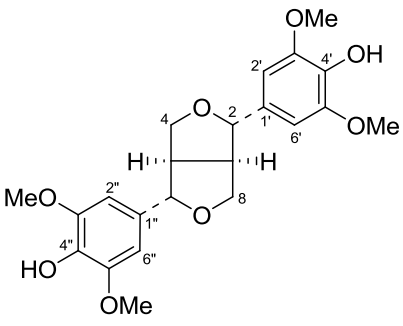

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Table 2.1: Alkaloid Composition of *L. griffithii*

Plant part	Alkaloid	Yield (g kg^{-1})
Stem-bark (13.8 kg)	Leucolusine (**1**) [New]	0.0002
	Leuconicine A (**2**) [New]	0.0297
	Leuconicine B (**3**) [New]	0.0379
	Leuconicine C (**4**) [New]	0.0034
	Leuconicine D (**5**) [New]	0.0033
	Leuconicine E (**6**) [New]	0.0034
	Leuconicine F (**7**) [New]	0.0016
	Leuconicine G (**8**) [New]	0.0007
	Leuconodine A (**9**) [New]	0.0017
	Leuconodine B (scholarisine G) (**10**) [New]	0.0012
	Leuconodine C (**11**) [New]	0.0004
	Leuconodine D (**12**) [New]	0.0005
	Leuconodine E (**13**) [New]	0.0003
	Leuconoxine (**14**)	0.0104
	Leuconodine F (6-oxoleuconoxine) (**15**)	0.0006
	Mersicarpine (**16**)	0.0040
	Arboloscine (**17**)	0.0037
	3,14-Dehydroleuconolam (**18**) [New]	0.0002
	Leuconolam (**19**)	0.1124
	O-Methylleuconolam (**20**)	0.0355
	Epi-leuconolam (**21**) or 6,7-dehydroleuconoxine (**21a**)	0.0005
	Nor-rhazinicine (**22**) [New]	0.0011
	5,21-Dihydrorhazinilam *N*-oxide (**23**) [New]	0.0004
	5,21-Dihydrorhazinilam (**24**)	0.0044
	Rhazinilam (**25**)	0.0628
	Rhazinal (**26**)	0.0019
	Rhazinicine (**27**)	0.0009
	(–)-Eburnamaline (**28**) [New]	0.0003
	(+)-Eburnamonine (**29**)	0.0016
	(+)-Eburnamenine (**30**)	0.0024
	O-Methylisoeburnamine (**31**)	0.0010
	O-Methyleburnamine (**32**)	0.0010
	(+)-Isoeburnamine (**33**)	0.0101

Table 2.1, continued

Plant part	Alkaloid	Yield (g kg^{-1})
	(−)-Eburnamine (**34**)	0.0113
	(±)-Vincamine (**35**)	0.0006
	Leucophyllidine (**36**) [New]	0.0008
	Leuconoline (**37**) [New]	0.0029
	Leucofoline (**38**) [New]	0.0004
	Leucoridine A (**39**) [New]	0.0004
	Leucoridine B (**40**) [New]	0.0004
	Leucoridine C (**41**) [New]	0.0003
	Leucoridine D (**42**) [New]	0.0006
	Tetrahydroalstonine (**43**)	0.0058
	17(*S*)-Ajmalicinial (**44**) and 17(*R*)-Ajmalicinial (**45**)	0.0012
	Akuammidine (**46**)	0.0032
	16(*R*)-19,20-*E*-Isositsirikine (**47**)	0.0029
	16(*S*)-19,20-*E*-Isositsirikine (**48**)	0.0009
	Z-Geissoschizol (**49**)	0.0003
	Fluorocarpamine (**50**)	0.0006
	Pleiocarpamine (**51**)	0.0290
	16-Hydroxymethylpleiocarpamine (**52**)	0.0016
	(−)-Isovallesiachotamine (**53**)	0.0011
	(−)-Isovallesiachotamine (**53**) and (+)-Vallesiachotamine (**54**)	0.0013
	Norfluorocurarine (**55**)	0.0008
	12-Hydroxynorfluorocurarine (**56**)	0.0033
	Tubotaiwine (**57**)	0.0262
	Tubotaiwine *N*-oxide (**58**)	0.0004
	N(4)-Chloromethyltubotaiwine chloride (**59**)	0.0137
	Venoterpine (**60**)	0.0005
	Syringaresinol (**61**) (lignan)	0.0087

2.1.1 Oxindole Alkaloids

2.1.1.1 Leucolusine (1)

Leucolusine (**1**)[136] was isolated in a very small amount as a light yellowish oil, $[\alpha]_D$ +55 ($CHCl_3$, *c* 0.12). The UV spectrum was characteristic of an unsubstituted oxindole chromophore showing absorption maxima at 206, 252, and 288 nm, while the IR spectrum showed bands at 3406, 3249 and 1716 cm^{-1}, suggesting the presence of OH, NH, and lactam functionalities, respectively. The EIMS of **1** showed a molecular ion peak at *m/z* 330, and HREIMS measurements established the molecular formula as $C_{19}H_{26}N_2O_3$, requiring 8 degrees of unsaturation. Strong fragment peaks were observed at *m/z* 182 (47%) and 168 (100%), which though initially puzzling, became intelligible after eventual unravelling of the overall structure (*vide infra*). The ^{1}H NMR spectrum of **1** (Figure 2.3) showed the presence of four aromatic hydrogens (δ 6.74–7.37), an indolic NH (δ 7.63), a broad downfield signal due to OH (δ 8.13), a relatively downfield one-H singlet due to H(21) (δ 4.29), and an ethyl side chain (δ 0.84; 1.37, 1.55). The ^{13}C NMR data (Table 2.2) showed a total of 19 carbon resonances (one methyl, eight methylene, five methine, and five quaternary carbons) in agreement with the molecular formula. The six aromatic carbon resonances can be readily assigned from consideration of their characteristic shifts as well as from the HMBC and NOE data (Figure 2.2). The observed NOE between the indolic NH and the aromatic doublet of doublets at δ 6.74 allowed the assignment of this resonance to H(12) and the lower field doublet of doublets at δ 7.37 to H(9). The three-bond correlations from H(9) and NH to the downfield quaternary signal at δ 77.3 indicated that this signal was due to C(7), which, from its downfield shift, suggested some form of oxygenation. The C(7) substituent was

deduced to be an OH from the IR, MS, and ^{1}H NMR data. Another downfield quaternary signal at δ 180.5 indicated the presence of an oxindole functionality, which received further support from the observed three-bond correlation from H(6) to the oxindole C(2). The COSY spectrum revealed three partial structures, *viz.*, an -NCH_2CH_2 fragment corresponding to NC(5)–C(6), an OCH_2CH_2 fragment corresponding to OC(16)–C(17), and an -$NCH_2CH_2CH_2$ fragment corresponding to NC(3)–C(14)–C(15). The latter fragment was deduced with the aid of HMBC (three-bond correlations from H(3) and H(21) to C(15)), as the H(15) resonances were partially overlapped with the H(14) and H(19) signals. The singlet observed at δ 97.7 was attributed to the isolated methine corresponding to C(21), its downfield shift due to it being linked to both a nitrogen (N(4)) and an oxygen atom.

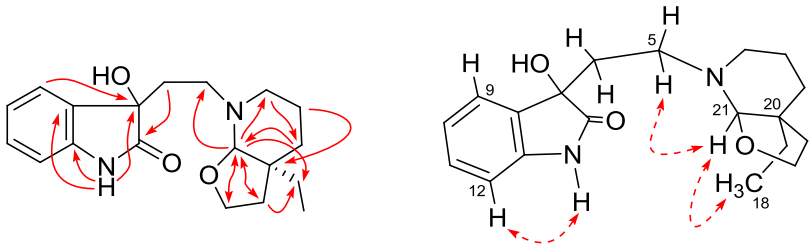
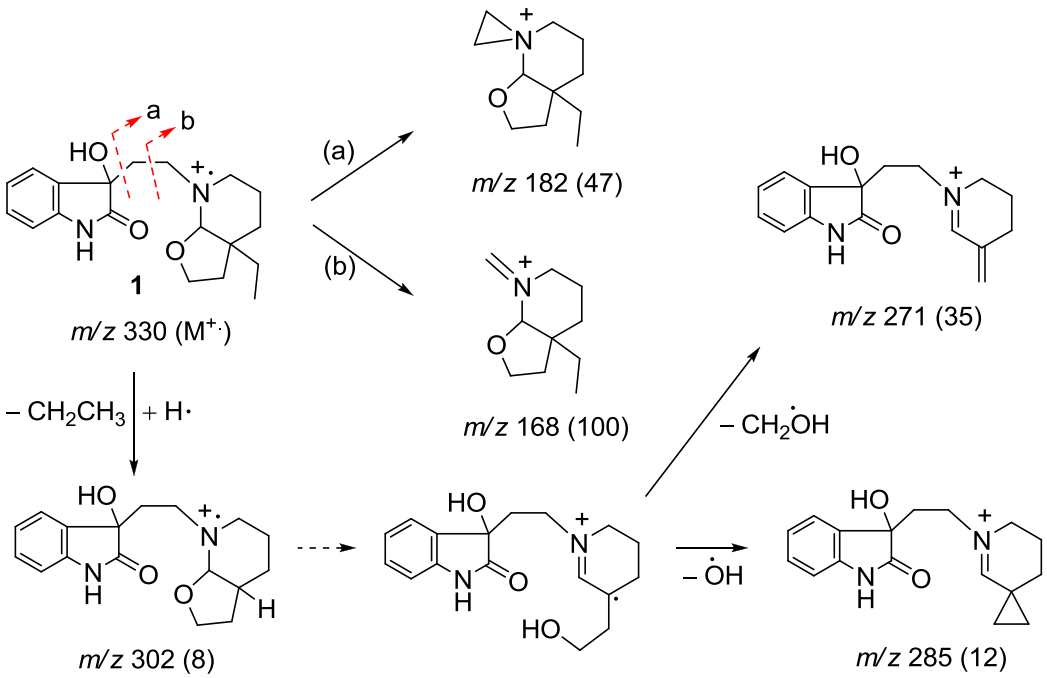


Figure 2.2: Selected HMBCs and NOEs of **1** (= HMBC; = NOE)

The above data permitted assembly of the complete structure of leucolusine (**1**). The C(7) hydroxy-substituted oxindole chromophore is attached *via* C(7) to one end of the C(5)–C(6) fragment, the other end being attached to N(4). This was supported by the observed HMBC correlations from H(6) to C(2), and from H(21) to C(5). The N(4) atom forms part of an ethyl substituted *cis*-fused piperidine-tetrahydrofuran ring (a 3a-ethyloctahydrofuro[2,3-*b*]pyridine unit) as indicated by the HMBC and NOE data. Thus, the three-bond correlations from H(21) to C(3), and from H(3) to C(21), indicated

connection of C(21) to N(4), while the observed three-bond correlation from H(14) to C(20) indicated attachment of C(15) to the quaternary C(20). The observed H(15)/C(21) and H(21)/C(15) correlations indicated that C(21) and C(20) are contiguous forming part of the piperidine ring. The observed correlation from H(16) to C(21) and from H(17) to C(21) permitted assembly of the tetrahydrofuran ring, *cis*-fused at C(20) and C(21), while the observed correlations from H(18) to C(20), and from H(17), H(21) to C(19), indicated attachment of the ethyl side-chain at the quaternary C(20). The *cis*-fusion of the piperidino-tetrahydrofuran rings was deduced from the observed NOE between H(18) and H(21) (Figure 2.2) which also fixes the relative configurations at C(20) and C(21). The structure thus unravelled is completely in agreement with the full HMBC and NOE data.

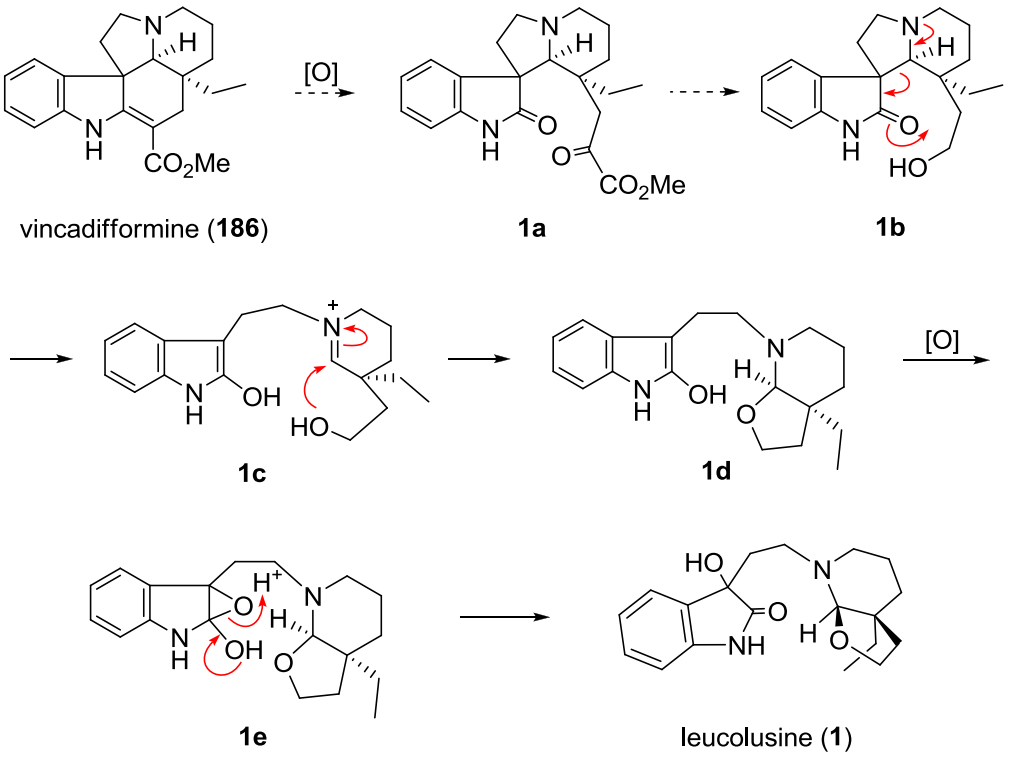


Scheme 2.1: Mass spectral fragmentation of **1**

The completed structure also permitted interpretation of the mass spectrum of leucolusine as shown in Scheme 2.1, in particular the origin of the strong fragments

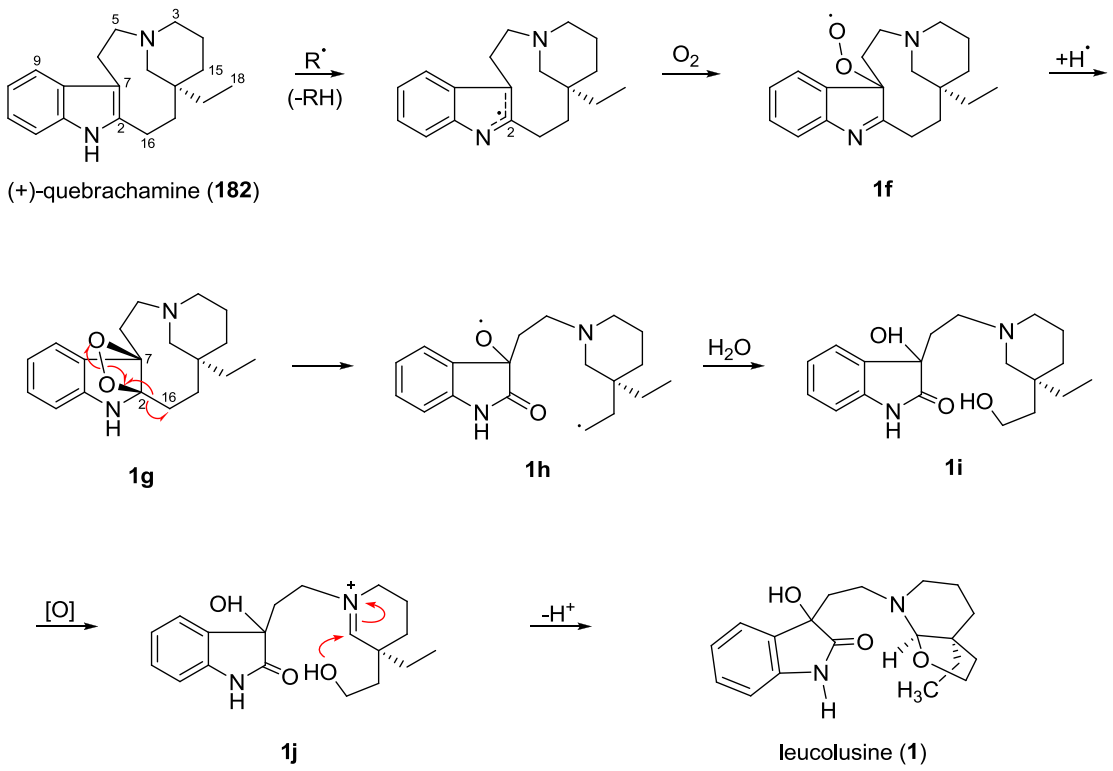
observed at *m/z* 168 and 182, due to scission of the C(5)–C(6) and C(6)–C(7) bonds, respectively.

A possible origin of this unusual ring-opened alkaloid is from an *Aspidosperma* precursor such as vincadifformine (**186**)[303] (Scheme 2.2). Oxidative cleavage of **186** gives the oxindole-ketoester **1a**, which on subsequent decarboxylation followed by reduction, gives the alcohol **1b**. A Grob-like, lone-pair assisted fragmentation of **1b** leads to cleavage of the C(7)–C(21) bond, furnishing the iminium ion **1c**, which on intramolecular trapping by OH yields the tetracyclic intermediate **1d**. Oxidation of **1d** gives the epoxide **1e**, which on subsequent oxidation at C(2) with concomitant epoxide ring-opening, leads to leucolusine (**1**). The proposed pathway leads to the relative configuration as shown in **1** although the available data does not allow assignment of the configuration at C(7).



Scheme 2.2: A possible biogenetic pathway to **1**

Another possible pathway to leucolusine (**1**) is from another *Aspidosperma* precursor, such as (+)-quebrachamine (**182**) (Scheme 2.3). Saturation of the C(2) carbon of (+)-quebrachamine (**182**) by a free radical followed by oxidative coupling gives the oxygen-radical adduct **1f**. Hydrogen abstraction by the oxygen-radical adduct **1f** furnishes the dioxetane intermediate **1g**. Homolytic cleavage of the weak O–O and C(2)–C(16) bonds of the dioxetane intermediate leads to the diradical oxindole intermediate **1h**, which is then followed by radical quenching to give the 7-hydroxy oxindole alkaloid **1i**. Oxidation of the oxindole alkaloid furnishes the iminium ion **1j**, which on intramolecular trapping by OH yields leucolusine (**1**).



Scheme 2.3: Another possible pathway to **1**[304]

Table 2.2: ^{1}H and ^{13}C NMR Spectroscopic Data of Leucolusine (**1**)[a]

Position	δ_H	δ_C	HMBC		DNOE/NOESY
			^{2}J	^{3}J	
2	–	180.5			
3	2.69 m	44.6	14	15, 21	
	2.69 m				
5	2.86 dt (13.5, 4)	50.2		21	21
	3.38 ddd (13.5, 11, 3)				
6	1.65 m	32.2		2	
	2.12 ddd (15, 11, 4)				
7	–	77.3			
8	–	132.3			
9	7.37 dd (7.6, 1)	124.1		7, 11, 13	
10	6.98 td (7.6, 1)	122.8		8, 12	
11	7.15 td (7.6, 1)	129.2		9, 13	
12	6.74 dd (7.6, 1)	110.2		8, 10	NH
13	–	140.0			
14	1.53 m	21.2		20	
	1.55 m				
15	1.35 m	26.9		3, 21	
	1.56 m				
16	3.83 td (9, 4)	64.1	17	21	
	3.94 dd (16.6, 9)				
17	1.60 m	35.1	16	15, 19, 21	
	1.75 m				
18	0.84 t (7.6)	8.9	19	20	21
19	1.37 m	27.0	18, 20	15, 17, 21	
	1.55 m				
20	–	42.4			
21	4.29 s	97.7		3, 5, 15, 16, 17, 19	5, 18
NH	7.63 s	–	13	7, 8	12
OH	8.13 br s	–			

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, HMBC, and NOESY/DNOE.

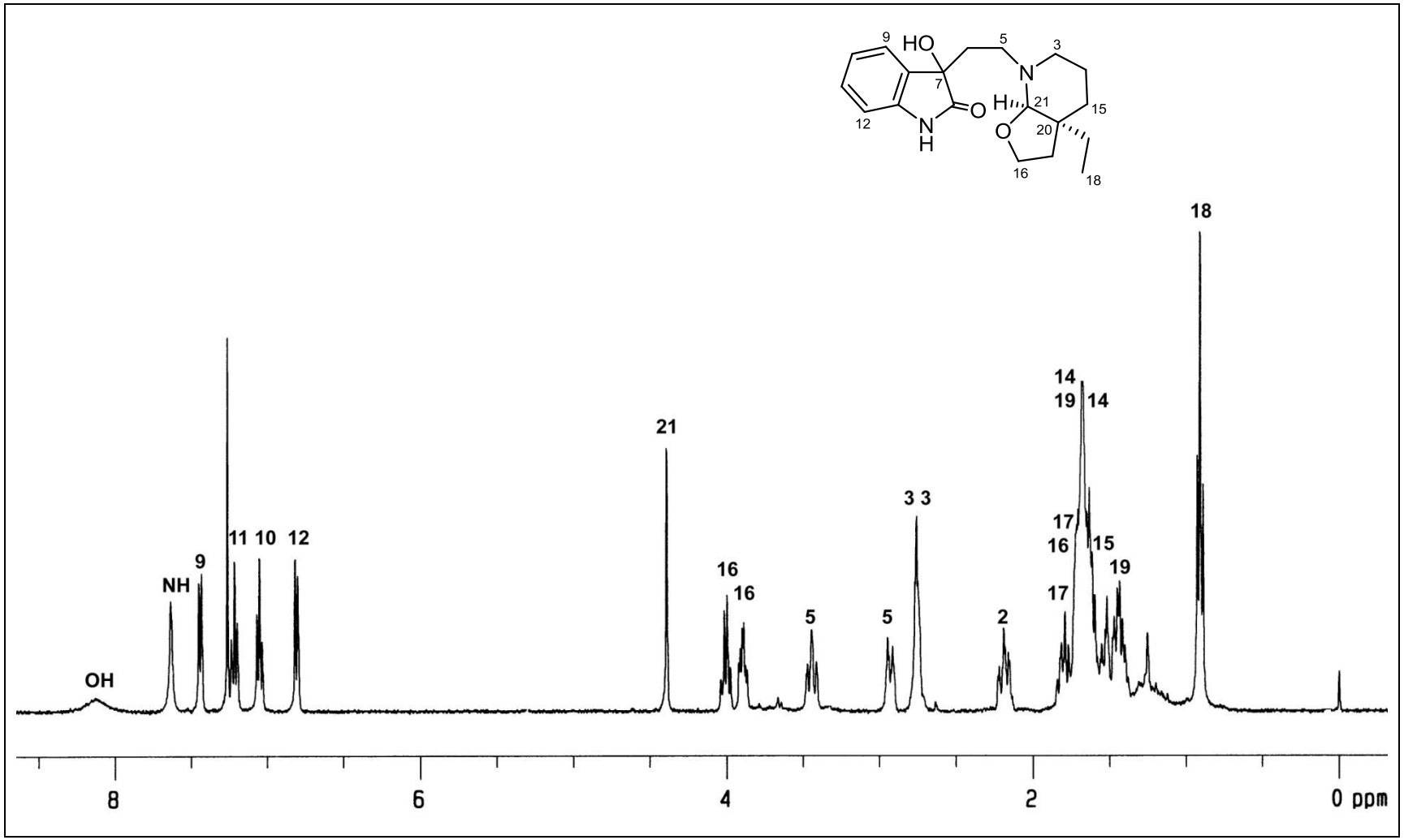


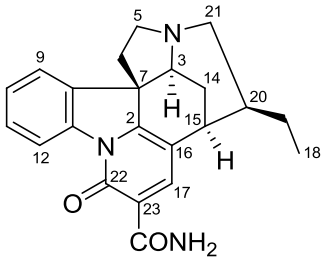
Figure 2.3: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leucolusine (**1**)

2.1.2 *Strychnos* Alkaloids

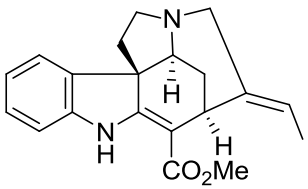
2.1.2.1 Leuconicine A (2)

Leuconicine A (**2**)[134,305] was obtained as a light yellowish oil, with $[\alpha]_D$ −473 ($CHCl_3$, *c* 0.24). The UV spectrum showed absorption maxima at 211, 282, and 369 nm, characteristic of a methyleneindoline chromophore. The IR spectrum (thin film) showed a broadened band at 3361 cm^{-1} due to an amide NH_2 function and another broad band at 1672 cm^{-1}, due probably to overlap of conjugated lactam carbonyl and the amide I (carbonyl) band, while the amide II (NH) band was observed at 1614 cm^{-1}. In $CHCl_3$ solution, the two primary amide NH stretching (symmetric and asymmetric) bands were both detected. The H-bonded NH stretching absorptions were seen at 3479 and 3299 cm^{-1}, while the free NH stretching vibrations were observed at 3684 and 3620 cm^{-1}. The lactam carbonyl and amide II signals were unchanged at 1674 and 1613 cm^{-1}. The EIMS of **2** showed a molecular ion at *m*/*z* 361, which was also the base peak, the odd mass indicating the presence of a third nitrogen atom. This was confirmed by HREIMS, which yielded the molecular formula $C_{22}H_{23}N_3O_2$ requiring 13 double-bond equivalents. Other notable fragment peaks were observed at *m*/*z* 332 (M–Et) and 288 (M–Et–$CONH_2$). The ^{13}C NMR data (Table 2.4) accounted for all of the 22 carbon resonances, comprising one methyl, five methylene, eight methine, and eight quaternary carbons. The presence of conjugated lactam and amide carbonyl functionalities was supported by the observed quaternary carbon signals at δ 161.1 and 165.8, respectively. The ^1H NMR spectrum (Figure 2.6) showed the presence of an unsubstituted aromatic moiety (δ 7.40, dd, *J* = 8, 1.3 Hz, H(9); 7.30, td, *J* = 8, 1.3 Hz, H(10); 7.38, td, *J* = 8, 1.3

Hz, H(11); 8.50, dd, *J* = 8, 1.3 Hz, H(12)), an olefinic singlet at δ 8.29, and an ethyl side chain (δ 1.06, t, *J* = 7.3 Hz, H(18); 1.28, m, H(19); 1.51, m, *J* = 7.3 Hz, H(19)). In addition, the signals due to the hydrogens of a primary amide group were observed as two distinct one-H doublets (*J* = 4 Hz) at δ 9.48 and 5.92. The two signals are mutually coupled, as shown by homonuclear decoupling, and both slowly exchanged on addition of D_2O (complete exchange required more than 24 h). The nonequivalence of these amide hydrogens is likely a consequence of a substantial barrier to rotation of the amide C–N bond as well as H-bonding, a phenomenon that has been encountered previously.[306,307]



2



89

The NMR data were suggestive of a strychnan derivative, such as for example, akuammicine (**89**), except for the presence of an ethyl in place of an ethylidene side chain, and the incorporation of an additional ring. The COSY and HMQC data disclosed partial structures that are consistent with the presence of an akuammicine type skeleton, *viz.*, NCH_2CH_2 and NCH_2CH, corresponding to the NC(5)–C(6) and NC(21)–C(20) units, respectively. The COSY spectrum also showed the presence of an $NCHCH_2$ fragment. This partial structure should in fact be part of the NC(3)–C(14)–C(15) fragment, but extensive overlap allowed only the NC(3)–C(14) fragment to be discerned. The presence of the C(15) methine as part of the NC(3)–C(14)–C(15) fragment linked from C(15) to C(20) can however be deduced from the three-bond correlations observed from H(3) and H(21) to C(15) in the HMBC spectrum. Additional

elements to be accounted for include a conjugated lactam carbonyl (δ_C 161.1), a trisubstituted alkene (δ_C 120.2, 145.4; olefinic H, δ_H 8.29), and a primary amide function. The lactam carbonyl must be attached to the indolic nitrogen N(1) from the observed deshielding of the aromatic H(12) (the observed reciprocal NOEs between H(9) (δ 7.40) and H(3) (δ 4.11) allowed the assignment of the aromatic signal at δ 8.50 as H(12)). Insertion of the trisubstituted double bond between this lactam carbonyl and C(16) results in the formation of the sixth ring (a 2-pyridone) and completes the assembly of the molecule.

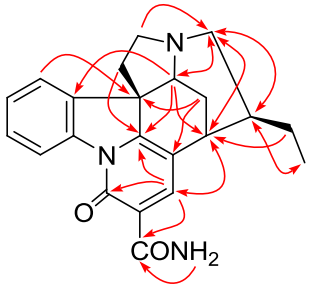


Figure 2.4: Selected HMBCs of **2**

Attachment of the olefinic methine, C(17) is to C(16) from the observed three-bond correlations from this hydrogen (H(17)) to C(2), C(15), and C(22), while the substitution of the amide function at C(23) is supported by the three-bond correlation from H(17) to the amide carbonyl as seen in the HMBC spectrum (Figure 2.4).

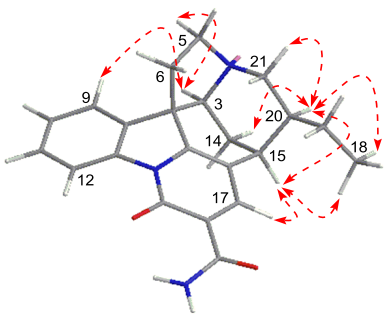
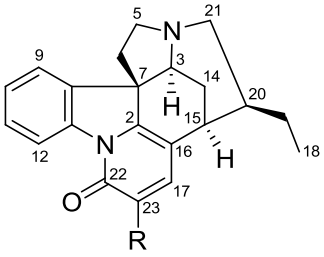
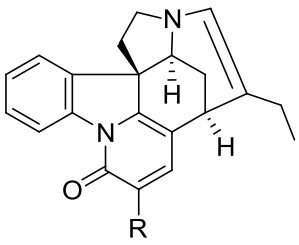


Figure 2.5: Selected NOEs of **2**

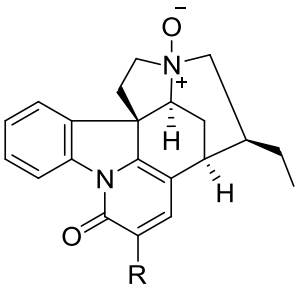
The relative configurations at the various stereogenic centers were established from NOEs (Figure 2.5) and analysis of the vicinal coupling constants. The reciprocal NOEs observed for H(9)/H(3) determined the relative configurations at C(7) and C(3), which in turn allowed the orientation of H(15) to be assigned as α, which is also in accord with the observed H(15)/H(17) NOE. The preferred chair conformation adopted by the piperidine ring D can be deduced from the absence of H(14*S*)/H(21α) NOEs,[308] as well as from analysis of the $J_{20\text{-}21}$ vicinal coupling constants. Thus, the observed $J_{20\text{-}21\beta}$ and $J_{20\text{-}21\alpha}$ values of 11 and 4 Hz, respectively, are consistent with the dihedral angles resulting from a β- or equatorially-oriented C(20) ethyl group (H(21β) and H(20α) *trans*-diaxial with the piperidine ring D in a chair conformation).[309] In addition, the NOEs observed for H(15)/H(20), H(18) and H(20)/H(14*S*), H(21α) are only consistent with β-ethyl substitution or an equatorially-oriented ethyl at C(20). The structure and relative stereochemistry of leuconicine A is therefore as shown in structure **2**.



2 R = $CONH_2$
3 R = CO_2Me



4 R = $CONH_2$
5 R = CO_2Me
6 R = COOH



7 R = $CONH_2$, N(4)→O
8 R = CO_2Me, N(4)→O

2.1.2.2 Leuconicine B (3)

Leuconicine B (**3**)[134,305] was obtained as a light yellowish oil with $[\alpha]_D$ −720 ($CHCl_3$, *c* 1.55). The UV spectrum (203, 279, and 374 nm) was similar to that of **2**, while the IR spectrum showed bands due to conjugated ester (1737 cm^{-1}) and lactam (1703 cm^{-1}) carbonyl functionalities. The mass spectrum of **3** showed a molecular ion at *m*/*z* 376 (base peak) which analyzed for $C_{23}H_{24}N_2O_3$, requiring 13 degrees of unsaturation. The ^{13}C NMR data of **3** showed a total of 23 carbon resonances including two methyl, five methylene, eight methine, and eight quaternary carbons. The ^{1}H (Table 2.3) and ^{13}C NMR (Table 2.4) data of **3** were generally similar to those of **2**, indicating the presence of an unsubstituted aromatic moiety, an olefinic singlet, a conjugated lactam function, and an ethyl side chain. Notable differences include the absence of the signals due to the amide hydrogens, and the presence instead of signals due to a methyl ester (δ_C 165.9, 52.4; δ_H 3.95), suggesting the replacement of the amide function in **2** by a methyl ester at C(23) in **3**. The HMBC data also indicated incorporation of the sixth (2-pyridone) ring branched from the indolic nitrogen, and in addition confirmed the substitution at C(23) by a methyl ester group. Thus, the resonance at δ 158.8 was assigned to C(22) (lactam) from the observed three-bond correlation from the olefinic H(17) to C(22), while the other carbonyl resonance was assigned to the ester carbonyl attached to C(23), from the observed three-bond correlations from H(17) and the ester methyl hydrogens to the carbonyl resonance at δ 165.9.

The relative configurations at the various stereogenic centers were established from the observed NOEs (which were similar to those seen in **2**, Figure 2.5) as well as from analysis of the coupling constants (Table 2.3), which showed that the configurations at

the stereogenic centers in **3** are similar to those in **2**. An alkaloid (alkaloid 376) with similar NMR (low-field) data was previously isolated from *L. griffithii* and *L. eugenifolia*, but with incorrect assignments of some of the ^{13}C NMR signals and without establishment of stereochemistry at the various stereogenic centers.[124]

2.1.2.3 Leuconicine C (4)

Compound **4**, leuconicine C,[134] was isolated as a light yellowish oil, $[\alpha]_D$ −374 ($CHCl_3$, *c* 0.22). The UV and IR spectra were similar to those of **2**, suggesting an akuammicine-type compound with similar functionalities, such as the presence of a primary amide group. The EIMS of **4** showed a molecular ion at *m*/*z* 359, and HREIMS measurements established the molecular formula as $C_{22}H_{21}N_3O_2$ (DBE 14). The ^{1}H and ^{13}C NMR data of **4** (Tables 2.3 and 2.4, respectively) were generally similar to those of **2** except for some differences. First, the ^{13}C NMR spectrum of **4** indicated the presence of an additional double bond from the resonances observed at δ 122.8 and 129.8, corresponding to olefinic quaternary and methine carbons, respectively. Comparison of the ^{13}C NMR spectrum with that of **2** showed that while the chemical shifts of the other carbons were essentially unchanged, those of C(20) and C(21) have undergone substantial shifts to the lower field sp^2 region, indicating that these carbons correspond to the site of the unsaturation. This was also supported by the observed two-bond correlation from H(21) to C(20), and the three-bond correlations from H(3) and H(15) to C(21) in the HMBC spectrum. The signal due to H(20) seen in the spectrum of **2** (δ 1.88) was absent in that of **4**. Instead, a new olefinic H signal corresponding to H(21) was observed as a singlet at δ 5.55 in the ^{1}H NMR spectrum of **4**, in place of the two

H(21) signals previously seen for **2** at δ 1.95 and 3.03. Corresponding changes have also occurred in the signals due to H(19), which in **4** are seen as a quartet (*J* = 7.3 Hz) at δ 2.14. These features are all consistent with the presence of a double bond across C(20) and C(21). Catalytic hydrogenation (H_2, Pd/C) of **4** yielded **2** as the sole product furnishing additional proof for the structure of leuconicine C (**4**).

2.1.2.4 Leuconicine D (5)

Leuconicine D (**5**)[134] was obtained as a light yellowish oil, with $[\alpha]_D$ –501 ($CHCl_3$, *c* 0.42). The UV and IR spectra of **5** were similar to those of **3**, indicating the presence of similar functionalities. The EIMS of **5** showed a molecular ion peak at *m/z* 374, and HREIMS measurements gave the molecular formula $C_{23}H_{22}N_2O_3$ (DBE 14). As in the case of **4** and **2**, comparison of the ^1H and ^{13}C NMR spectroscopic data of **5** and **3** (Tables 2.3 and 2.4, respectively) indicated that **5** is the 20,21-dehydro congener of **3**. The C(20) and C(21) olefinic signals of **5** were seen at δ 122.6 and 129.9, respectively, and the vinylic H(21) signal was seen as a singlet at δ 5.55. The assignment of the vinylic singlet to H(21) was consistent with the observed two-bond correlation from H(21) to C(20), and the three-bond correlation from H(3) to C(21) in the HMBC spectrum.

As in the case of **4**, catalytic hydrogenation of **5** proceeded smoothly to furnish **3** as the sole product. These facile hydrogenations (**4** to **2** and **5** to **3**) provided additional support for the configurational assignments of **2** and **3** as hydrogenation was seen to proceed from the less hindered concave or α-face.

Table 2.3: ^{1}H NMR Spectroscopic Data of Leuconicines A–D (**2**–**5**)[a]

H	**2**	**3**	**4**	**5**
3	4.11 m	4.18 m	4.21 m	4.19 m
5β	2.90 m	2.95 m	3.18 dd (12, 6.4)	3.18 dd (12, 6.4)
5α	3.17 m	3.23 m	3.30 td (12, 4.4)	3.29 td (12, 4.5)
6α	2.02 m	2.01 m	1.86 dd (12, 4.4)	1.85 dd (12, 4.5)
6β	2.94 m	2.92 m	2.28 td (12, 6.4)	2.29 m
9	7.40 dd (8, 1.3)	7.39 dd (8, 1)	7.49 dd (8, 1)	7.44 dd (7.5, 1)
10	7.30 td (8, 1.3)	7.28 td (8, 1)	7.34 td (8, 1)	7.30 td (7.5, 1)
11	7.38 td (8, 1.3)	7.36 td (8, 1)	7.42 td (8, 1)	7.41 td (7.5, 1)
12	8.50 dd (8, 1.3)	8.56 dd (8, 1)	8.57 dd (8, 1)	8.65 dd (7.5, 1)
14*R*	1.38 dt (13, 3)	1.43 dt (13, 3)	1.33 dt (13, 3)	1.35 m
14*S*	2.21 dt (13, 3)	2.24 dt (13, 3)	2.28 m	2.29 m
15	2.92 m	2.88 m	3.12 m	3.05 m
17	8.29 s	7.91 s	8.48 s	8.12 s
18	1.06 t (7.3)	1.07 t (7.3)	1.07 t (7.3)	1.77 t (7.4)
19	1.28 m	1.29 m	2.14 q (7.3)	2.14 q (7.4)
	1.51 m	1.47 m	2.14 q (7.3)	2.14 q (7.4)
20	1.88 m	1.93 m	–	–
21β	1.95 t (11)	2.01 t (11)	5.55 s	5.55 s
21α	3.03 dd (11, 4)	3.09 dd (11, 4)		
OMe	–	3.95 s	–	3.95 s
NH	5.92 d (4)	–	6.30 d (4.4)	–
	9.48 d (4)		9.51 d (4.4)	

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, and NOESY/DNOE.

Table 2.4: ^{13}C NMR Spectroscopic Data of Leuconicines A–D (**2**–**5**)[a]

C	**2**	**3**	**4**	**5**
2	161.6	162.0	161.2	159.3
3	62.2	62.1	59.9	59.9
5	54.4	54.3	53.5	53.5
6	44.8	44.7	46.0	46.0
7	55.5	55.5	56.5	56.7
8	139.9	139.3	139.8	139.4
9	120.2	119.9	120.5	120.3
10	127.0	126.6	127.0	126.7
11	128.1	128.2	128.3	128.4
12	117.5	117.7	117.8	118.1
13	140.6	140.8	140.5	140.7
14	31.3	31.2	30.8	30.8
15	36.3	35.9	33.6	33.6
16	115.7	113.9	119.3	118.7
17	145.4	145.9	142.9	143.7
18	11.5	11.4	12.8	12.8
19	26.4	26.3	27.4	27.5
20	38.7	38.5	122.8	122.6
21	51.4	51.3	129.8	129.9
22	161.1	158.8	158.2	158.6
23	120.2	120.0	120.8	120.3
CO_2*Me*	–	52.4	–	52.2
CO_2Me	–	165.9	–	166.0
CONH_2	165.8	–	166.1	–

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

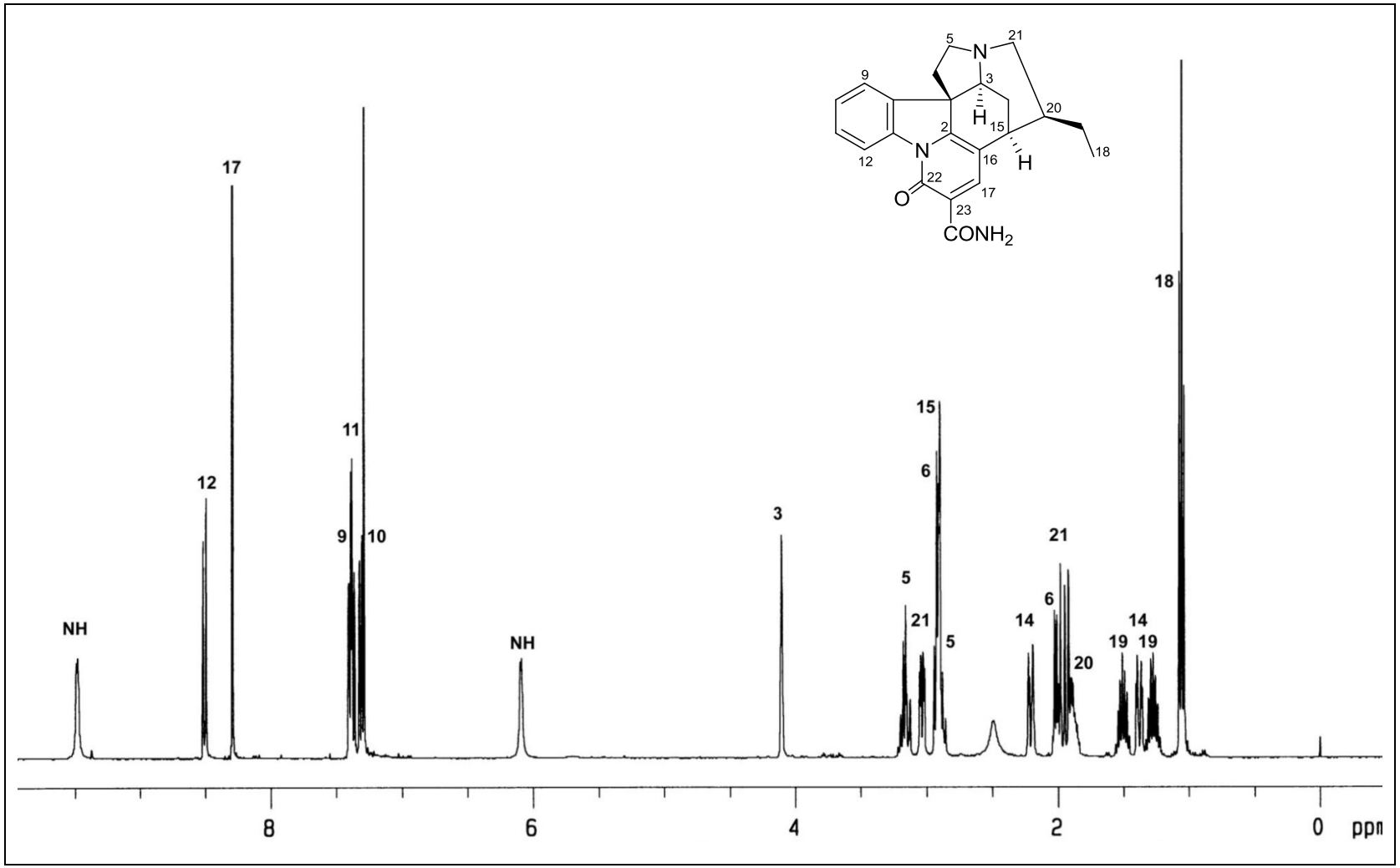


Figure 2.6: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconicine A (**2**)

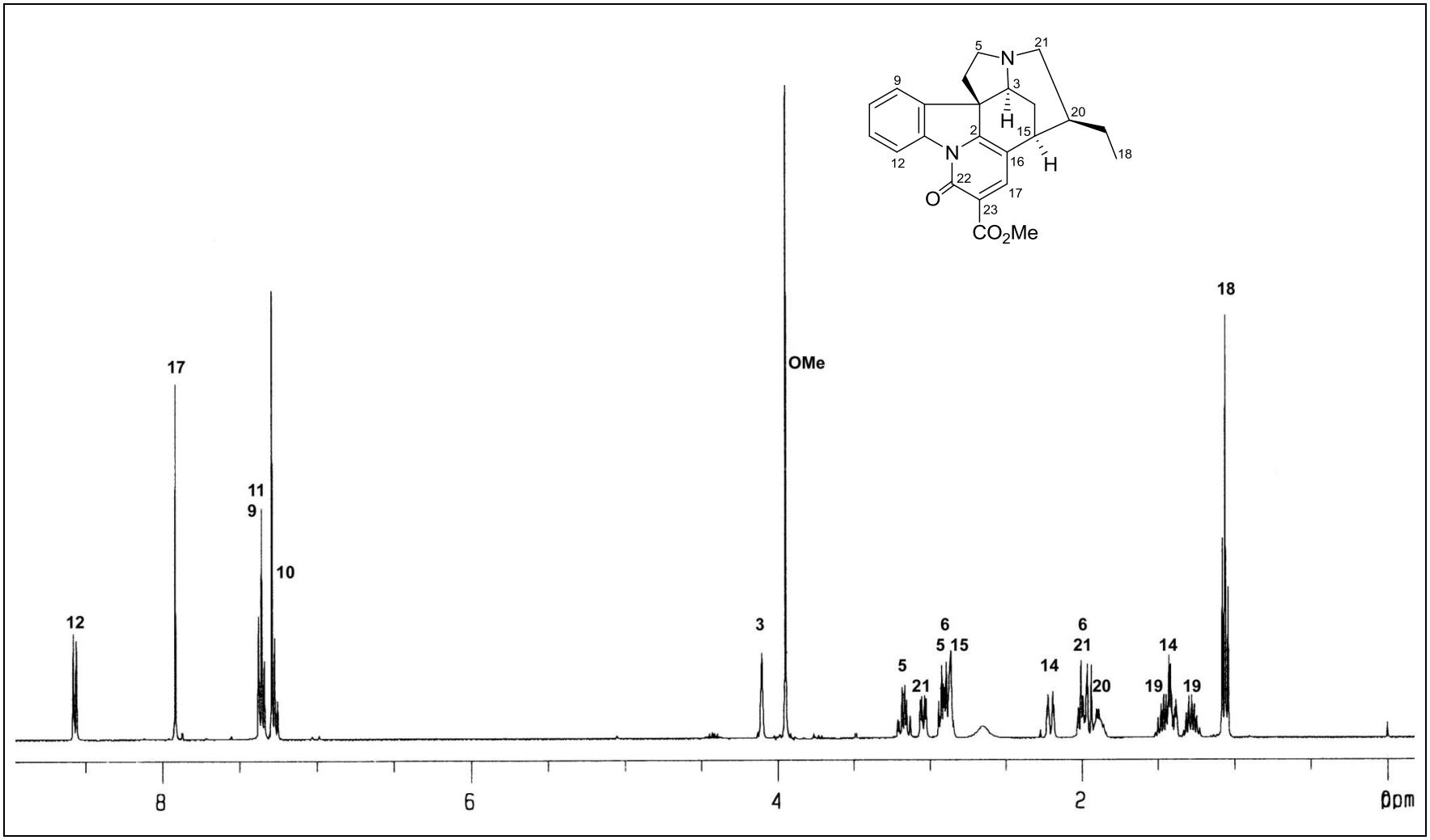


Figure 2.7: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconicine B (**3**)

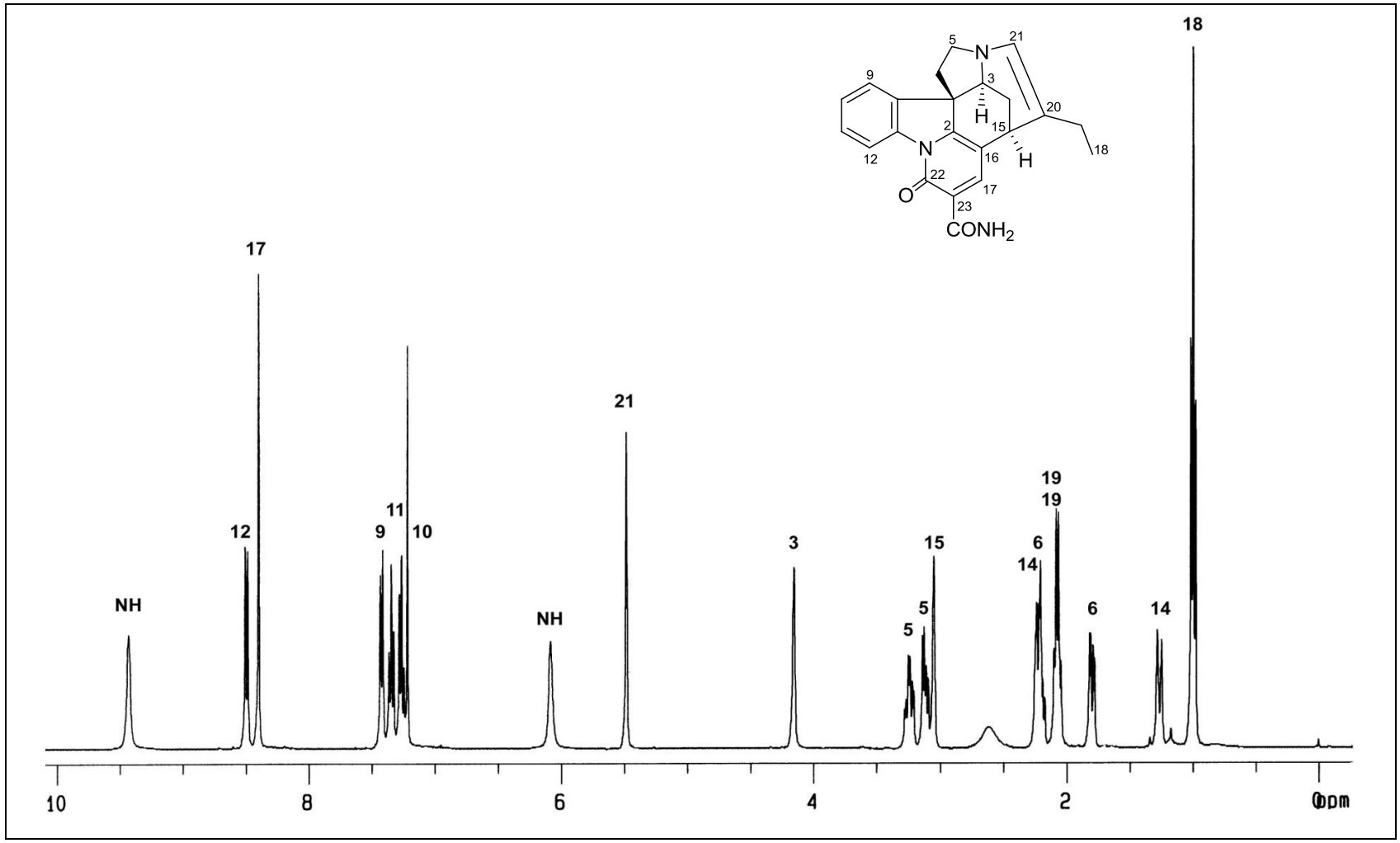


Figure 2.8: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconicine C (**4**)

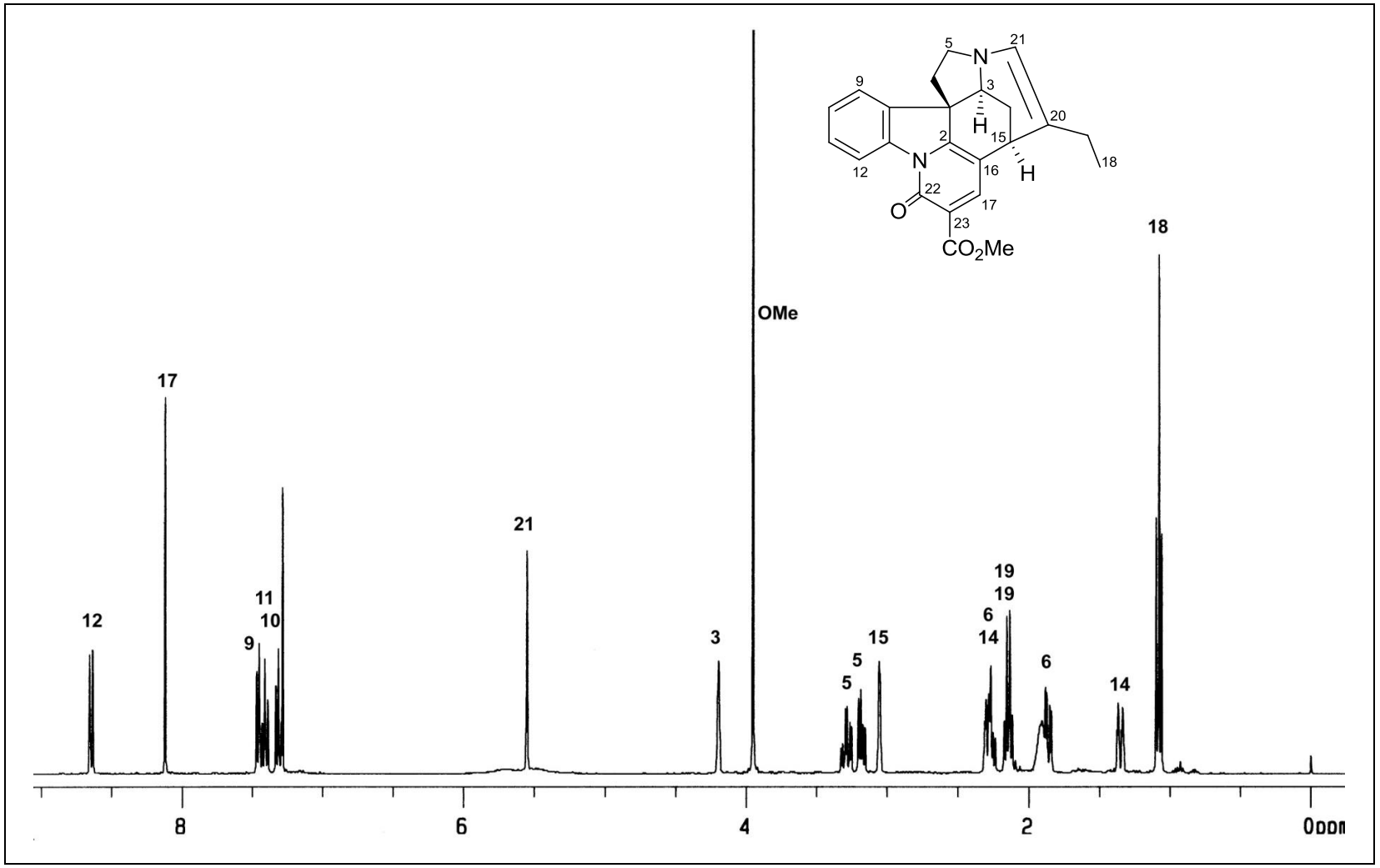


Figure 2.9: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconicine D (**5**)

2.1.2.5 Leuconicine E (6)

Leuconicine E (**6**)[134] was isolated as a light yellowish oil, with $[\alpha]_D$ −193 ($CHCl_3$, *c* 0.04). The EIMS showed in addition to the M^+ ion peak at *m/z* 360, a fragment peak due to M–CO_2 at *m*/*z* 316. HREIMS measurements established the molecular formula as $C_{22}H_{20}N_2O_3$. The UV spectrum of **6** was similar to those of **2**–**5**, while the IR spectrum showed broadened bands at 3457 and 1728 cm^{-1}, due to OH and acid/lactam carbonyl functionalities, respectively. The ^1H and ^{13}C NMR data (Tables 2.5 and 2.6, respectively) of **6** were also generally similar to those of **4** and **5**, indicating the presence of an unsubstituted aromatic moiety (δ 7.52, dd, *J* = 8, 1 Hz, H(9); 7.40, td, *J* = 8, 1 Hz, H(10); 7.47, td, *J* = 8, 1 Hz, H(11); 8.55, dd, *J* = 8, 1 Hz, H(12)), two isolated olefinic hydrogens (singlets at δ 5.58 and 8.44), two trisubstituted double bonds (δ 122.4, 143.9; 122.7, 130.2), and an ethyl side chain (δ 1.08, t, *J* = 7.3 Hz, H(18); 2.15, q, *J* = 7.3 Hz, H(19)). Two downfield quaternary carbon signals were also observed at δ 159.7 and 166.0, of which the former was assigned to the lactam carbonyl C(22) from the observed three-bond correlation from H(17) to this carbon. A notable departure in the ^1H NMR data (Table 2.5) of **6** compared with those of compounds **2**–**5** was the absence of signals due either to the methyl ester CH_3 singlet or the amide NH_2 doublets, which were observed in the previous four compounds. In their place however, a low field one-H broad singlet (exchanged with D_2O) was observed at δ 14.31, suggesting the presence of an acid function. Since the carbonyl resonance observed at δ 166.0 was not associated with ester or amide groups, it must be associated with the carboxylic acid group. The observed three-bond correlation from H(17) to the carboxyl carbon confirmed the substitution of C(23) by the carboxylic acid group.

2.1.2.6 Leuconicine F (7)

Leuconicine F (**7**)[134] was obtained as a light yellowish oil, with $[\alpha]_D$ –353 ($CHCl_3$, *c* 0.19). The EIMS showed the highest mass fragment at *m/z* 361 which corresponds to the fragment ion from loss of oxygen, a behavior characteristic of alkaloid *N*-oxides. The molecular ion could be detected by ESIMS which showed an MH^+ peak at *m/z* 378. HRESIMS measurements gave the formula $C_{22}H_{24}N_3O_3$, 16 mass units higher than that of **2**. The UV and IR spectra were similar to those of **2** while the NMR data of **7** showed a close resemblance to those of **2**, except for the downfield shifts of the carbon resonances for C(3), C(5), and C(21). Similarly the H(3), H(5), and H(21) signals have undergone downfield shifts compared to those in **2**. Compound **7** was therefore readily identified as the *N*(4)-oxide of **2**.

2.1.2.7 Leuconicine G (8)

Leuconicine G (**8**)[134] was obtained as a light yellowish oil, with $[\alpha]_D$ –265 ($CHCl_3$, *c* 0.06), and UV and IR spectra which were similar to those of **3**. As in the case of **7**, compound **8** was readily identified as the *N*(4)-oxide of **3** based on the ESIMS data (MH^+ *m/z* 393, $C_{23}H_{25}N_2O_4$) and the characteristic downfield shifts of the C(3), C(5), and C(21) resonances, and the corresponding H(3), H(5), and H(21) resonances, in the ^{13}C and ^{1}H NMR spectra, respectively, when compared to those of **3**.

Table 2.5: ^{1}H NMR Spectroscopic Data of Leuconicines E–G (**6**–**8**)[a]

H	**6**	**7**	**8**
3	4.25 m	4.50 m	4.45 m
5β	3.22 dd (12, 6.5)	3.65 dd (12, 8)	3.65 dd (12, 8)
5α	3.33 td (12, 4)	3.86 td (12, 9)	3.84 td (12, 9)
6α	1.90 dd (12, 4)	2.29 dd (15, 8)	2.28 dd (15, 8)
6β	2.31 dd (12, 6.5)	2.58 m	2.51 m
9	7.52 dd (8, 1)	7.52 dd (8, 1)	7.45 dd (8, 1)
10	7.40 td (8, 1)	7.37 td (8, 1)	7.34 td (8, 1)
11	7.47 td (8, 1)	7.46 td (8, 1)	7.44 td (8, 1)
12	8.55 dd (8, 1)	8.50 dd (8, 1)	8.55 dd (8, 1)
14*R*	1.36 dt (13, 3)	1.45 ddd (14, 4, 3)	1.46 m
14*S*	2.34 m	2.85 dt (14, 3)	2.84 ddd (14, 3, 2)
15	3.16 m	3.07 m	3.03 m
17	8.44 s	8.31 s	7.90 s
18	1.08 t (7.3)	1.11 t (7.3)	1.11 t (7.3)
19	2.15 q (7.3)	1.28 m	1.29 m
	2.15 q (7.3)	1.51 m	1.47 m
20	–	2.52 m	2.57 m
21β	5.58 s	3.02 t (13)	3.03 t (12)
21α		3.56 dd (13, 4.4)	3.55 dd (12, 5)
OMe	–	–	3.96 s
NH	–	6.32 d (4.4)	–
		9.33 d (4.4)	
OH	14.31 br s	–	–

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, and NOESY/DNOE.

Table 2.6: ^{13}C NMR Spectroscopic Data of Leuconicines E–G (**6**–**8**)[a]

C	**6**	**7**	**8**
2	159.7	161.3	158.5
3	60.0	74.7	75.0
5	53.6	67.4	68.1
6	46.3	39.8	39.9
7	57.1	51.5	51.7
8	139.8	137.6	137.3
9	120.8	120.5	120.0
10	128.0	127.6	127.3
11	128.8	129.5	129.6
12	118.4	117.8	118.0
13	139.9	139.9	140.2
14	30.9	27.1	27.2
15	33.9	34.4	34.5
16	116.1	114.7	113.1
17	143.9	144.9	145.2
18	12.8	11.0	11.1
19	27.5	24.9	25.0
20	122.7	34.4	34.4
21	130.2	64.9	65.2
22	163.1	156.9	157.8
23	122.4	122.0	122.0
CO_2*Me*	–	–	52.6
CO_2Me	–	–	165.1
CONH_2	–	165.3	–
CO_2H	166.0	–	–

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

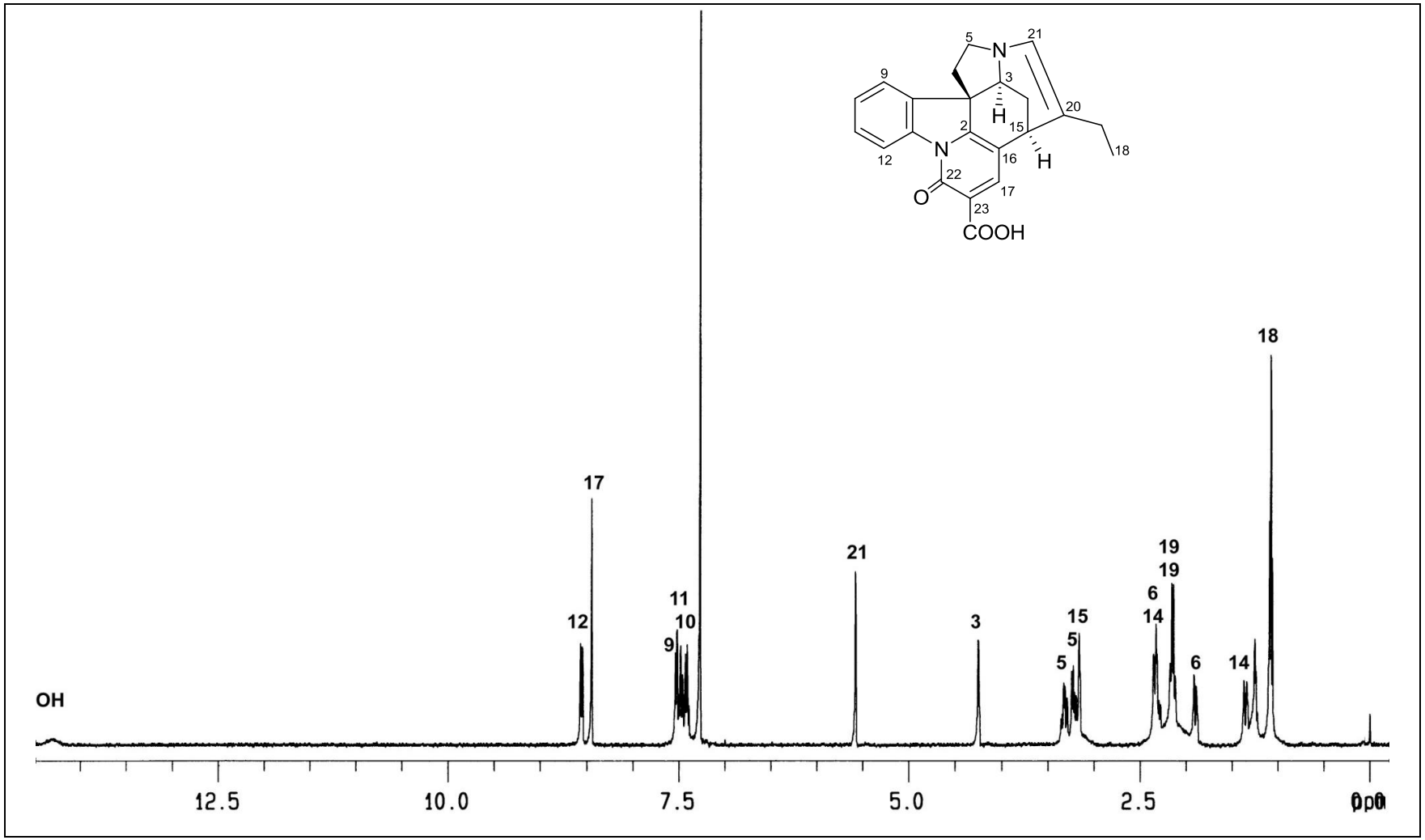


Figure 2.10: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconicine E (**6**)

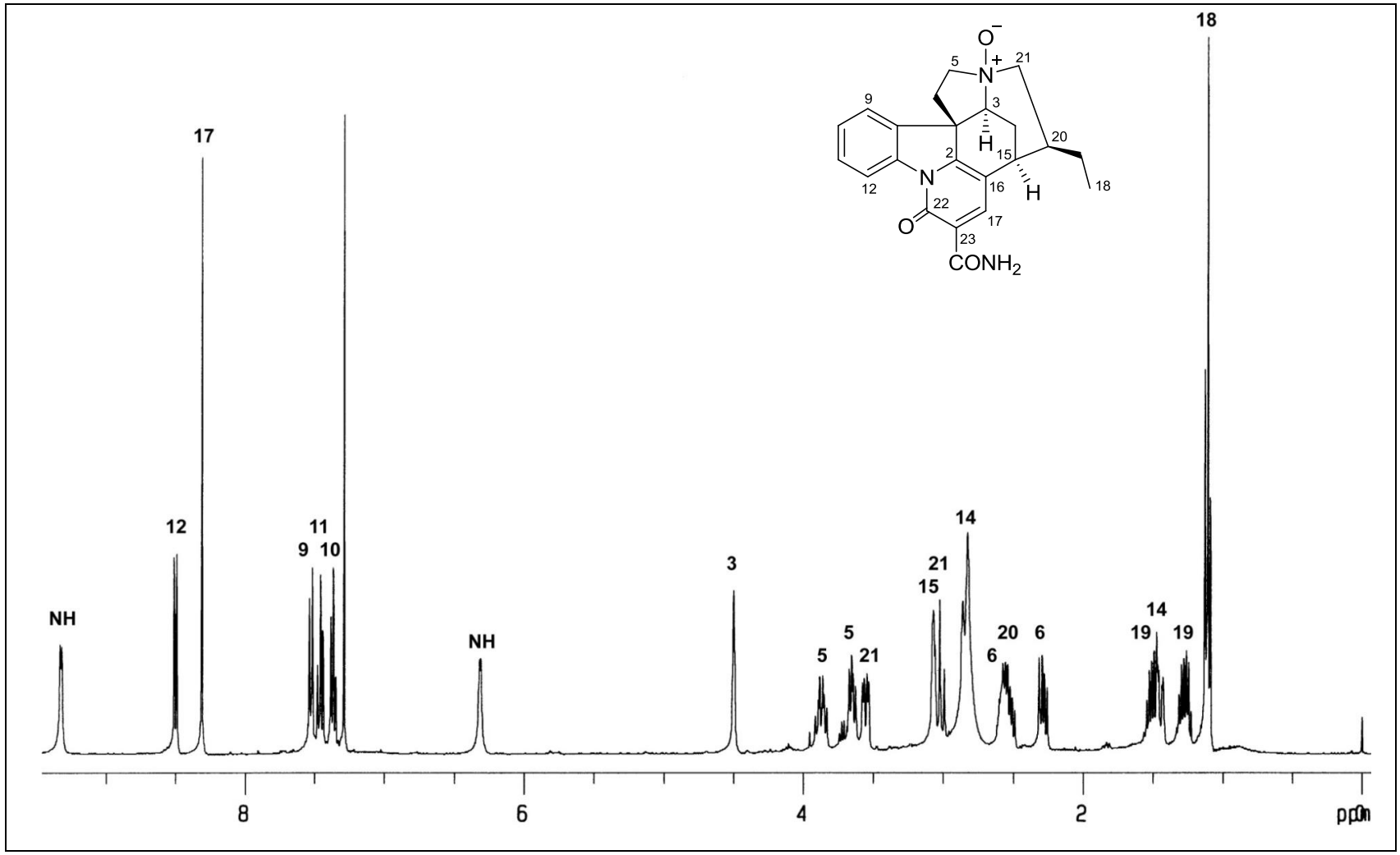


Figure 2.11: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconicine F (**7**)

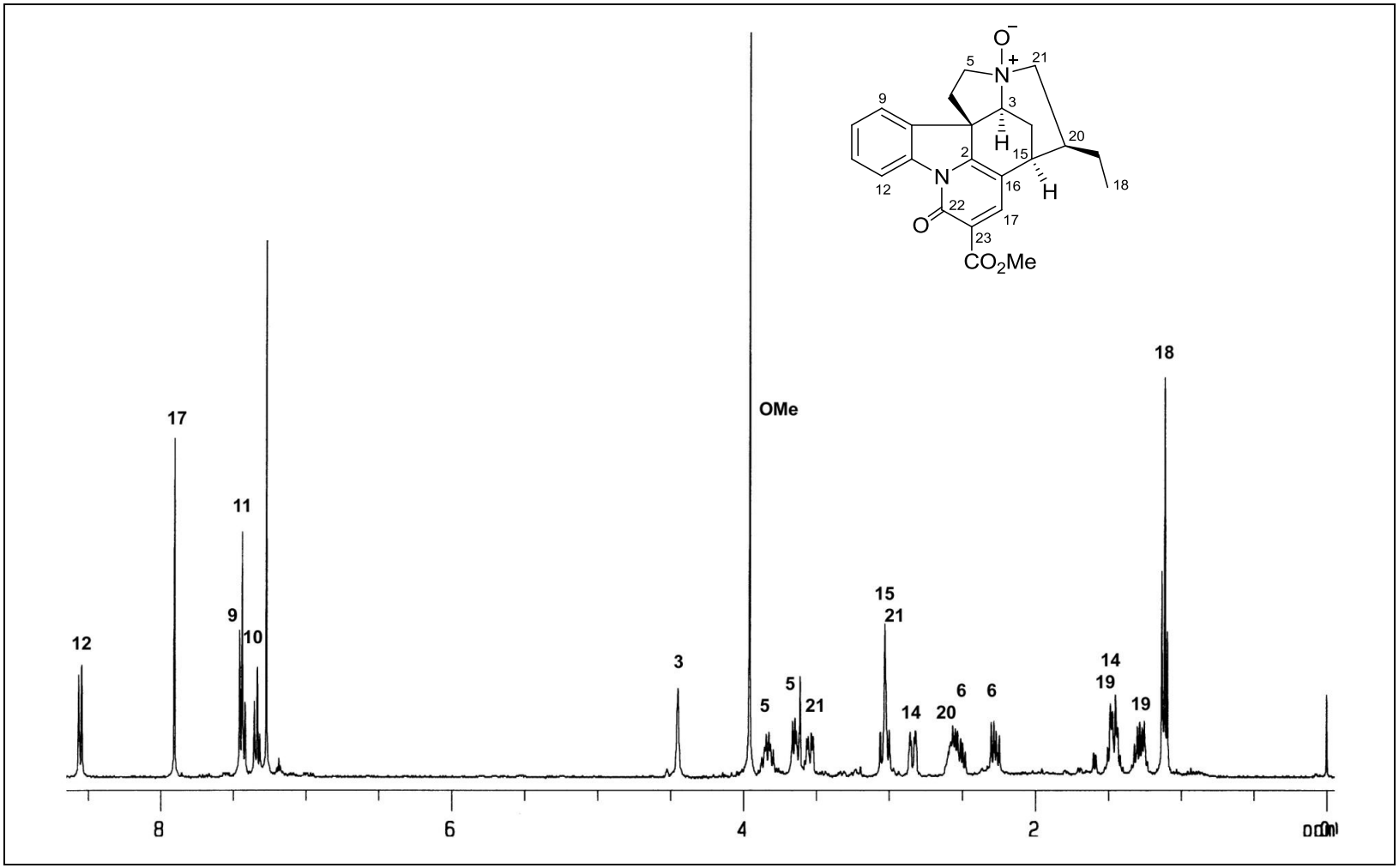
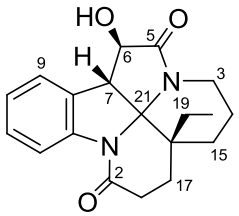


Figure 2.12: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconicine G (**8**)

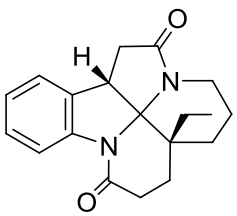
2.1.3 Leuconoxine–Leuconolam–Rhazinilam Alkaloids

2.1.3.1 Leuconodine A (9)

Leuconodine A (**9**) was isolated as a light yellowish oil, and subsequently crystallized from EtOH as colorless needles, mp 135–138 ^{o}C, with $[\alpha]_D$ –20 ($CHCl_3$, *c* 0.26). The UV spectrum showed absorption maxima at 242 and 277 nm, while the IR spectrum showed bands at 3346 and 1677 cm^{-1}, suggesting the presence of OH, and lactam functionalities, respectively. The EIMS of **9** showed a molecular ion peak at *m/z* 326, and HREIMS measurements established the molecular formula as $C_{19}H_{22}N_2O_3$, requiring 10 degrees of unsaturation. The ^{13}C NMR data (Table 2.8) showed a total of 19 carbon resonances (one methyl, six methylene, six methine, and six quaternary carbons) in agreement with the molecular formula. The observed quaternary carbon resonances at δ 172.0 and 173.1 are consistent with the presence of two lactam functionalities.



9



14

Detailed examination of the NMR data of **9** indicated a close similarity to that of leuconoxine (**14**),[128] except for some differences. The ^{1}H NMR spectrum (Figure 2.16) of **9** showed the presence of two additional methine singlets at δ 3.90 and 4.51, a broad

singlet at δ 5.11, and the absence of the characteristic benzylic H(7) doublet at δ 3.82 when compared to the spectrum of **14**. The methine singlet at δ 3.90 was assigned to C(7), based on the observed three-bond correlations from H(7) to C(5) and C(9) in the HMBC spectrum. The remaining methine singlet at δ 4.51, together with the corresponding oxymethine at δ 75.1, suggested oxygenation at C(6). The presence of the OH group was indicated by the broad singlet observed at δ 5.11 in the ^{1}H NMR spectrum, as well as from the absorption band at 3346 cm^{-1} in the IR spectrum. The placement of the OH substituent at C(6) was further supported by the observed three-bond correlation from H(6) to the doubly spirocyclic C(21) in the HMBC spectrum.

The relative configuration at C(6) was deduced to be *R* (H(6α)), from the observed reciprocal NOEs between H(9) and H(6). Compound **9** is therefore leuconodine A or 6β-hydroxyleuconoxine. The structure of **9** was further confirmed by X-ray diffraction analysis (Figure 2.13).

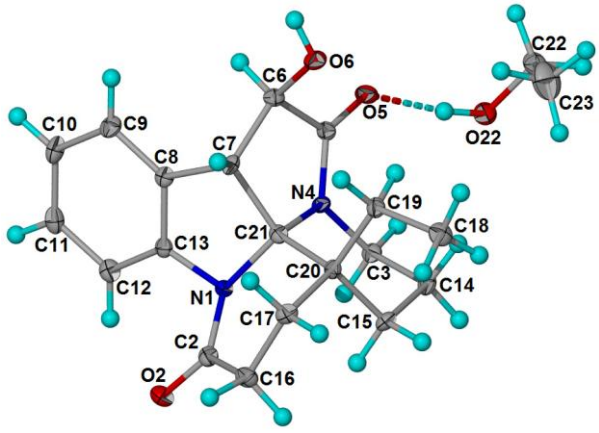
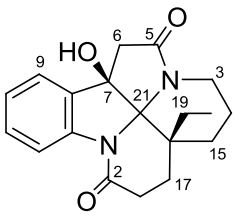


Figure 2.13: X-ray crystal structure of **9**

2.1.3.2 Leuconodine B (10)

Leuconodine B (**10**)[310] was isolated as a light yellowish amorphous solid, and subsequently crystallized from CH_2Cl_2–MeOH as colorless block crystals, mp 198–200 ^oC, with $[\alpha]_D$ –48 ($CHCl_3$, *c* 0.14). The UV and IR spectra of **10** were similar to those of **9**, suggesting a leuconoxine-type[128] compound with similar functionalities, such as the presence of OH, and lactam functionalities. The EIMS of **10** showed a molecular ion peak at *m/z* 326, and HREIMS measurements established the molecular formula as $C_{19}H_{22}N_2O_3$, indicating that **10** is isomeric to **9**. The ^1H and ^{13}C NMR spectroscopic data of **10** (Tables 2.7 and 2.8, respectively) were similar in all respects to those of **9** except for the chemical shifts involving H(6) and H(7). The two methine singlets corresponding to H(6) and H(7) seen in the ^1H NMR spectrum of **9** were absent in that of **10**. Instead, a pair of AB doublets was observed at δ 2.89 and 2.97 (*J* = 17 Hz; δ_C 42.2) in the ^1H NMR spectrum of **10**, suggesting the presence of an isolated methylene in **10**.



10

This observation has led to the placement of the OH substituent at C(7), while the AB doublets were assigned to the two H(6). This assignment received additional support from the observed downfield shift of the C(7) signal to δ 81.9 in **10**, compared to δc 49.6 observed for C(7) in **9**. The HMBC data further confirmed the site of oxygenation

at C(7) from the observed three-bond correlation from H(9) to C(7). Compound **10** is therefore leuconodine B (or 7-hydroxyleuconoxine).

Since, suitable crystals were obtained, an X-ray diffraction analysis (Figure 2.14) was carried out (X-ray analysis by Y. Y. Low) which confirmed the structure deduced based on the spectroscopic data.

During the course of this study, an alkaloid (scholarisine G) corresponding to **10** was reported from *Alstonia scholaris* from Yunnan, China.[310]

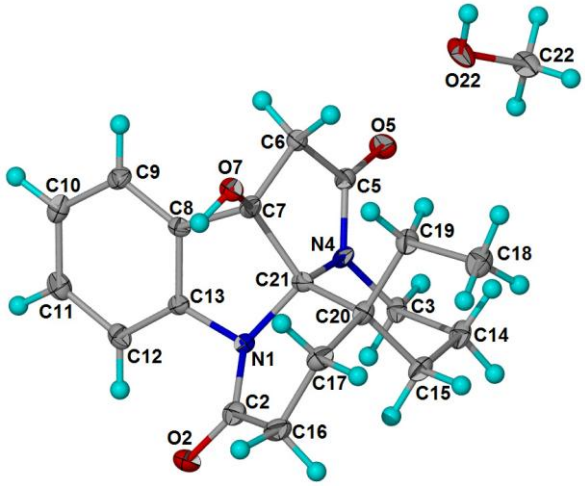


Figure 2.14: X-ray crystal structure of **10**

2.1.3.3 Leuconodine C (11)

Leuconodine C (**11**) was isolated in minute amounts as a light yellowish oil, $[\alpha]_D$ −71 ($CHCl_3$, *c* 0.24). The UV and IR spectra of **11** were similar to those of **9**. The ESIMS of **11** showed an $[M + H]^+$ peak at *m/z* 327, and HRESIMS measurements established the molecular formula as $C_{19}H_{22}N_2O_3$, indicating that **11** is isomeric with **9**. The ^1H and ^{13}C NMR spectroscopic data of **11** (Tables 2.7 and 2.8, respectively) were generally similar to those of leuconoxine (**14**), except for the aromatic region. Detailed examination of the ^{13}C NMR data indicated downfield shift of an aromatic signal to δ 155.0, suggesting oxygenation of one of the aromatic carbons of **11**. The most deshielded signal at δ 7.49 (*J* = 8.6 Hz) in the ^1H NMR spectrum (Figure 2.18) of **11** was assigned to H(12), due to anisotropy of the proximate lactam carbonyl function at C(2). This feature is common in all the other leuconoxine-type compounds. Analysis of the vicinal coupling constants of the remaining two aromatic signals, allowed the assignment of the signal at δ 6.64 (*J* = 8.6, 2 Hz) to H(11) and the signal at δ 6.60 (*J* = 2 Hz) to H(9). The COSY and HSQC data also revealed the presence of a CHCH unit, corresponding to the C(11)–C(12) fragment, consistent with a 10-hydroxy substituted leuconoxine (**14**).

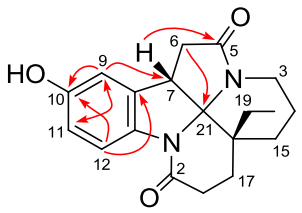


Figure 2.15: Selected HMBCs of **11**

The HMBC data (Figure 2.15) further confirmed the placement of the OH group at C(10) from the observed three-bond correlations from H(9) to C(7) and C(11), H(11) to C(9), and from H(12) to C(10). The structure deduced is entirely consistent with the rest of the HMBC data. Compound **11** is therefore leuconodine C (or 10-hydroxyleuconoxine).

Table 2.7: ^{1}H NMR Spectroscopic Data of Leuconodines A–C (**9**–**11**)[a]

H	**9**	**10**	**11**
3	2.89 ddd (13, 11, 4)	2.63 td (13, 3.4)	2.70 m
	3.99 ddd (13, 4)	3.92 br d (13)	3.86 br d (12)
6	4.51 s	2.89 d (17) α	2.56 d (17) α
		2.97 d (17) β	2.77 dd (17, 7) β
7	3.90 s	–	3.69 d (7)
9	7.27 dd (7.8, 1)	7.31 d (7.6)	6.60 d (2)
10	7.13 td (7.8, 1)	7.17 t (7.6)	–
11	7.25 td (7.8, 1)	7.34 t (7.6)	6.64 dd (8.6, 2)
12	7.87 dd (7.8, 1)	7.76 d (7.6)	7.49 d (8.6)
14	1.70 m	1.50 m	1.53 m
	1.70 m	1.63 m	1.53 m
15	1.64 m	1.68 m	1.59 m
	1.92 m	1.94 td (13, 3.4)	1.89 ddd (14, 12, 5)
16	2.53 ddd (19, 6, 1.4)	2.45 dd (19, 6)	2.41 dd (19, 5)
	2.78 ddd (19, 14, 6)	2.73 ddd (19, 13, 6)	2.65 m
17	1.60 m	1.68 m	1.59 m
	1.94 m	2.18 m	1.78 dd (14, 5)
18	0.90 t (7.3)	0.91 t (7.3)	0.86 t (7)
19	1.49 dq (13, 7.3)	1.77 dq (14, 7.3)	1.29 dq (13, 7)
	1.96 m	2.15 m	1.68 dq (13, 7)
OH	5.11 br s	3.28 br s	–

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, and NOESY/DNOE.

Table 2.8: ^{13}C NMR Spectroscopic Data of Leuconodines A–C (**9**–**11**)[a]

C	**9**	**10**	**11**
2	173.1	173.6	173.6
3	36.8	36.8	37.0
5	172.0	170.0	171.6
6	75.1	42.2	37.7
7	49.6	81.9	42.2
8	132.1	137.4	134.3
9	124.5	122.9	111.3
10	125.4	125.6	155.0
11	128.3	129.4	114.4
12	119.6	120.7	121.0
13	141.9	141.3	136.5
14	19.4	20.0	20.2
15	27.3	27.2	26.6
16	30.2	29.5	29.3
17	27.5	25.5	27.0
18	7.7	6.9	7.4
19	28.5	22.4	26.3
20	36.7	39.1	38.3
21	93.5	90.4	93.1

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

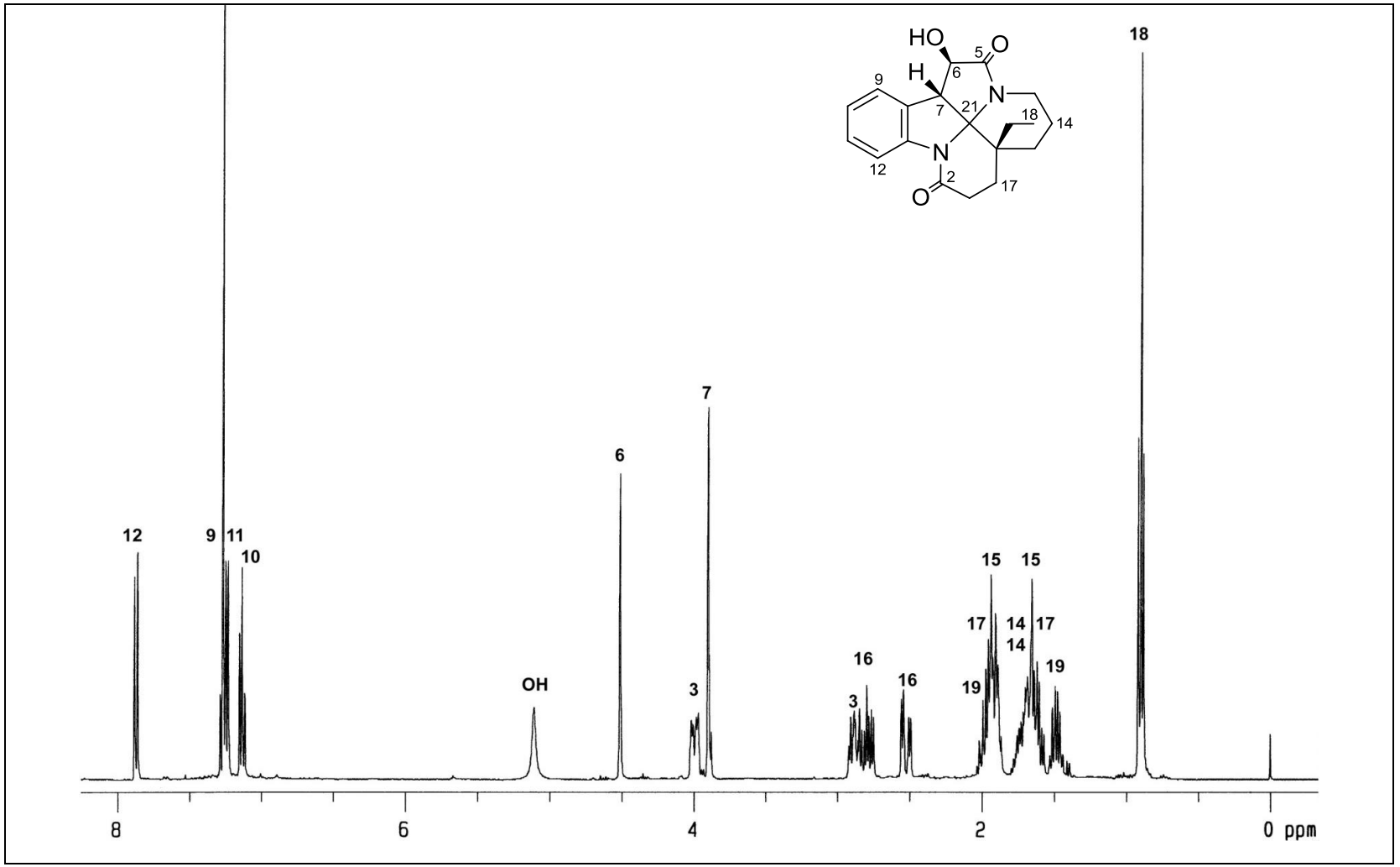


Figure 2.16: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconodine A (**9**)

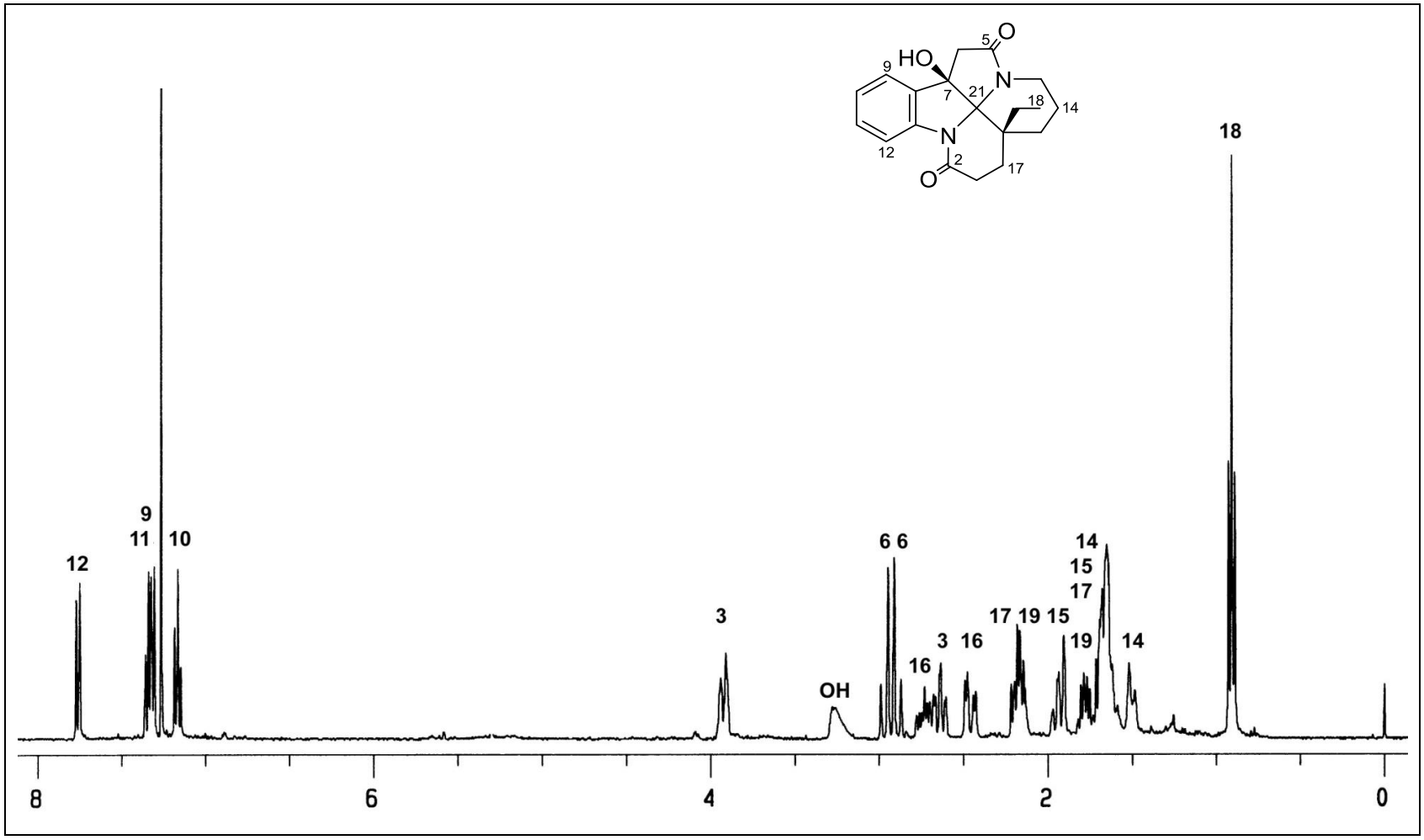


Figure 2.17: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconodine B (**10**)

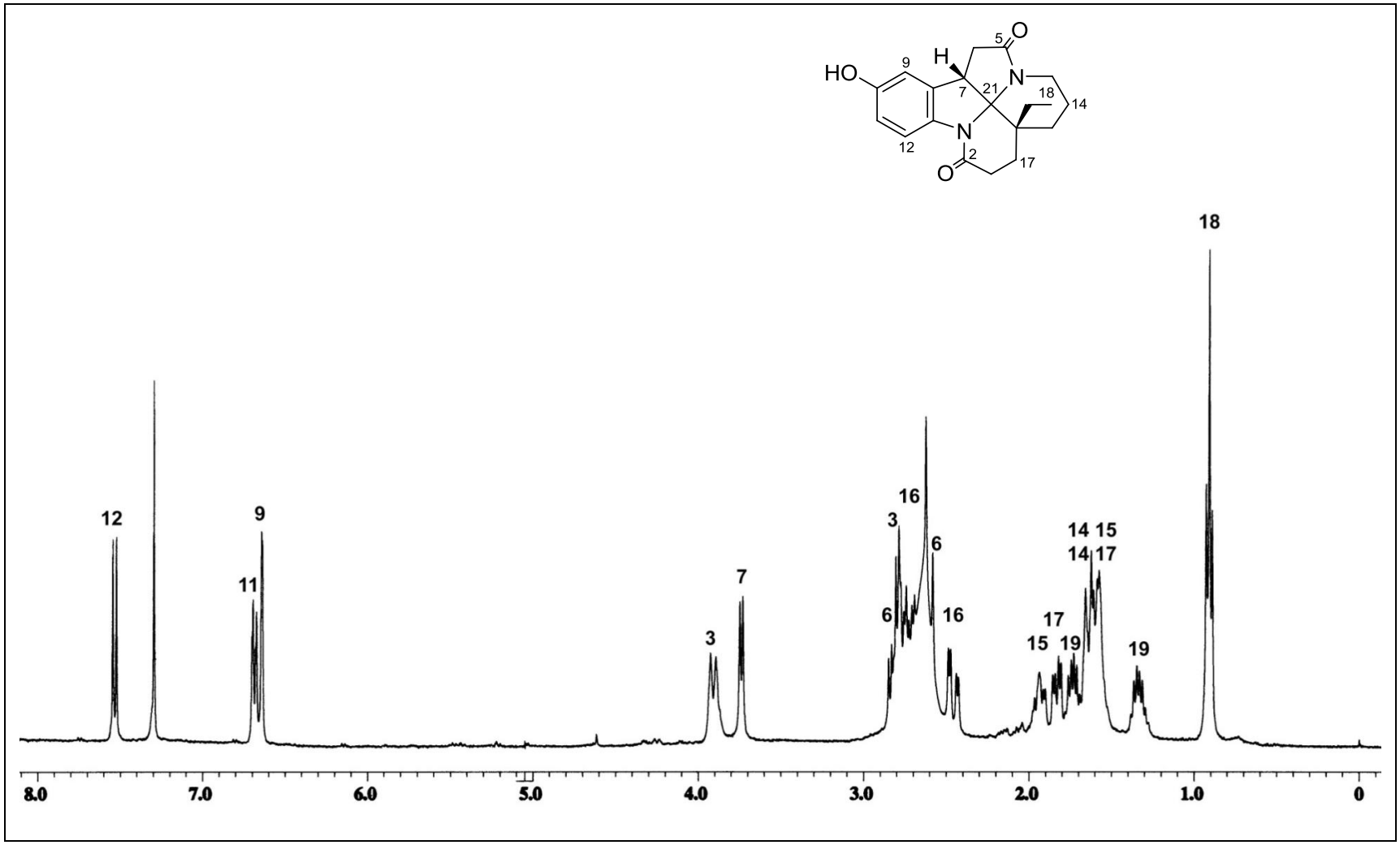
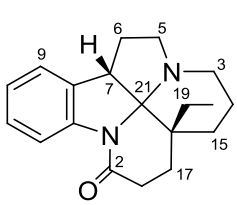


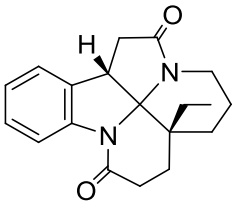
Figure 2.18: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconodine C (**11**)

2.1.3.4 Leuconodine D (12)

Leuconodine D (**12**) was obtained in small amounts as a light yellowish oil and subsequently as light yellowish crystals from CH_2Cl_2–MeOH, mp 100–105 ^oC, $[\alpha]_D$ –37 ($CHCl_3$, *c* 0.10). The UV spectrum showed absorption maxima at 210, 253, 283, and 376 nm, while the IR spectrum showed a band at 1670 cm^{-1} due to a lactam carbonyl function. The EIMS of **12** showed a molecular ion peak at *m/z* 296, and HREIMS measurements established the molecular formula as $C_{19}H_{24}N_2O$. The ^1H NMR data of **12** (Table 2.9) were essentially similar to those of leuconoxine (**14**),[128] except for the upfield shifts of the proton resonances due to H(3), H(6), H(18), and H(19). The ^{13}C NMR data (Table 2.9) of **12** were essentially similar to those of **14**, except for the absence of the signal due to one lactam carbonyl and the presence instead of a methylene signal at δ 52.2 in **12**.



12



14

Analysis of the COSY and HMQC data of **12** revealed the presence of some fragments which were also present in leuconoxine (**14**), such as $NCH_2CH_2CH_2$, CH_2CH_2, and CH_2CH_3, corresponding to the NC(3)–C(14)–C(15), C(16)–C(17), and C(19)–C(18) units, respectively. However, an additional fragment was observed, *viz*., NCH_2CH_2CH in the COSY spectrum of **12**, which was assigned to NC(5)–C(6)–C(7), indicating that the lactam carbonyl function at C(5) had been replaced by an aminomethylene carbon.

This is consistent with the observed upfield shifts of some of the proton resonances in the ^{1}H NMR spectrum (Figure 2.21) of **12** (*vide supra*).

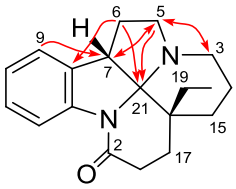
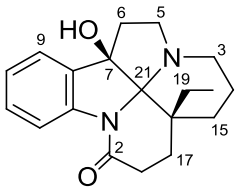


Figure 2.19: Selected HMBCs of **12**

The HMBC data (Figure 2.19) provided further confirmation for the methylene corresponding to C(5) from the observed three-bond correlations from H(3) to C(5), H(5) to C(3), C(7) and C(21), and from H(7) to C(5). The structure deduced is entirely consistent with the rest of the HMBC data. Compound **12** is therefore leuconodine D (or 5-deoxoleuconoxine).[311,312]

2.1.3.5 Leuconodine E (13)

Leuconodine E (**13**) was obtained in minute amounts as a light yellowish amorphous solid and subsequently as colorless crystals from CH_2Cl_2–MeOH, mp >230 ^{o}C, $[\alpha]_D$ −13 ($CHCl_3$, *c* 0.03). The UV spectrum of **13** was similar to that of **12**, while the IR spectrum showed bands due to OH (3416 cm^{-1}) and lactam (1636 cm^{-1}) functions. The EIMS of **13** showed a molecular ion peak at *m/z* 312, 16 mass units higher than that of **12**, and HREIMS measurements established the molecular formula as $C_{19}H_{24}N_2O_2$.



13

The ^{1}H NMR data of **13** (Table 2.9) showed a close resemblance to those of **12**, except for the absence of the characteristic benzylic H(7) seen at δ 3.77 in **12**. Comparison of the ^{13}C NMR data of **13** with that of **12** showed that while the chemical shifts of the other carbons were essentially unchanged, the signal due to C(7) has undergone substantial shift to the lower field region at δ 91.8, indicating that the site of oxygen substitution is at C(7).

This was also supported by the observed three-bond correlations from H(5) and H(9) to C(7) in the HMBC spectrum. Since suitable crystals of **13** were obtained, an X-ray diffraction analysis was also carried out which provided further confirmation of the structure deduced from analysis of the spectroscopic data (Figure 2.20).

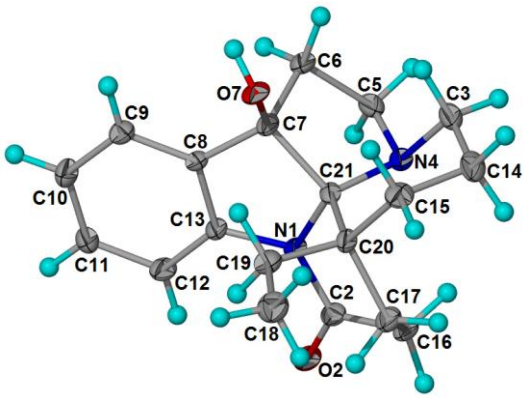


Figure 2.20: X-ray crystal structure of **13**

Table 2.9: ^{1}H and ^{13}C NMR Spectroscopic Data of Leuconodines D–E (**12**–**13**)[a]

Position	**12**		**13**	
	δ_H	δ_C	δ_H	δ_C
2	–	172.6	–	173.2
3	2.52 td (12, 3.5)	50.9	2.96 m	49.5
	3.03 br d (13)		2.96 m	
5β	2.72 dd (13, 6.5)	52.2	2.70 m	49.6
5α	2.93 td (13, 6.5)		2.87 m	
6α	1.50 dd (13, 6.5)	33.3	2.08 dd (11, 6)	44.4
6β	2.60 m		2.74 m	
7	3.77 d (9.5)	47.0	–	91.8
8	–	133.7	–	135.6
9	7.13 br d (7.3)	127.5	7.27 br d (8)	120.6
10	7.00 td (7.3, 1)	123.5	7.08 td (8, 1.5)	123.8
11	7.16 td (7.3, 1)	123.5	7.23 td (8, 1.5)	128.9
12	8.11 br d (7.3)	114.5	8.11 br d (8)	115.2
13	–	143.0	–	141.2
14	1.61 m	19.9	1.70 m	20.5
	1.82 m		1.80 m	
15	1.21 td (13, 3.5)	32.0	1.74 m	29.6
	1.79 m		1.74 m	
16	2.34 ddd (14, 5, 2.5)	32.8	2.31 dt (14, 3)	31.9
	3.59 td (14, 8)		3.53 ddd (14, 12, 10)	
17	1.70 m	28.9	1.77 m	32.3
	1.73 m		1.77 m	
18	0.73 t (7.3)	7.4	0.74 t (7.6)	7.4
19	1.07 dq (13, 7.3)	31.4	1.14 dq (14, 7.6)	28.9
	1.30 dq (13, 7.3)		1.74 m	
20	–	40.3	–	41.5
21	–	97.6	–	95.3

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

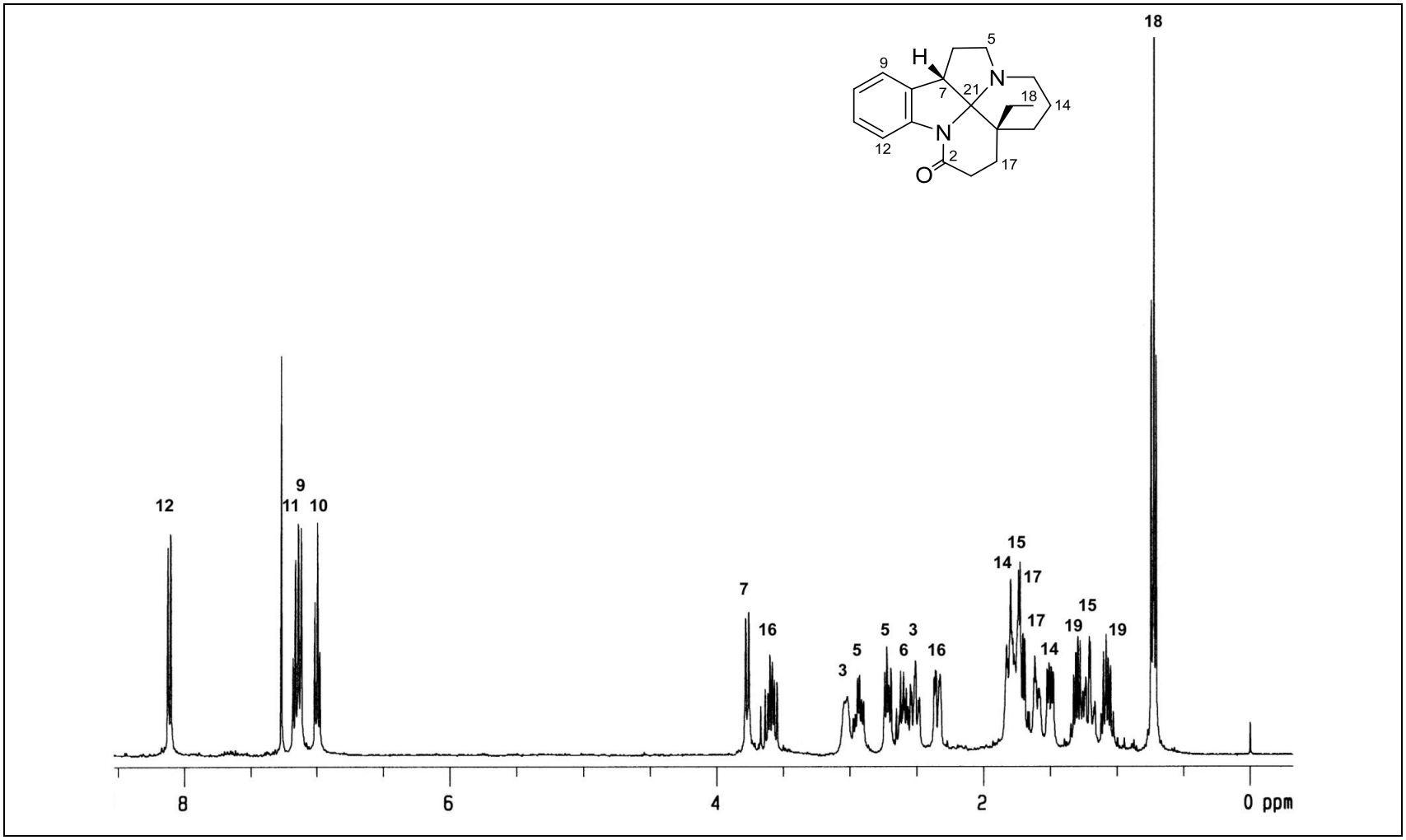


Figure 2.21: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconodine D (**12**)

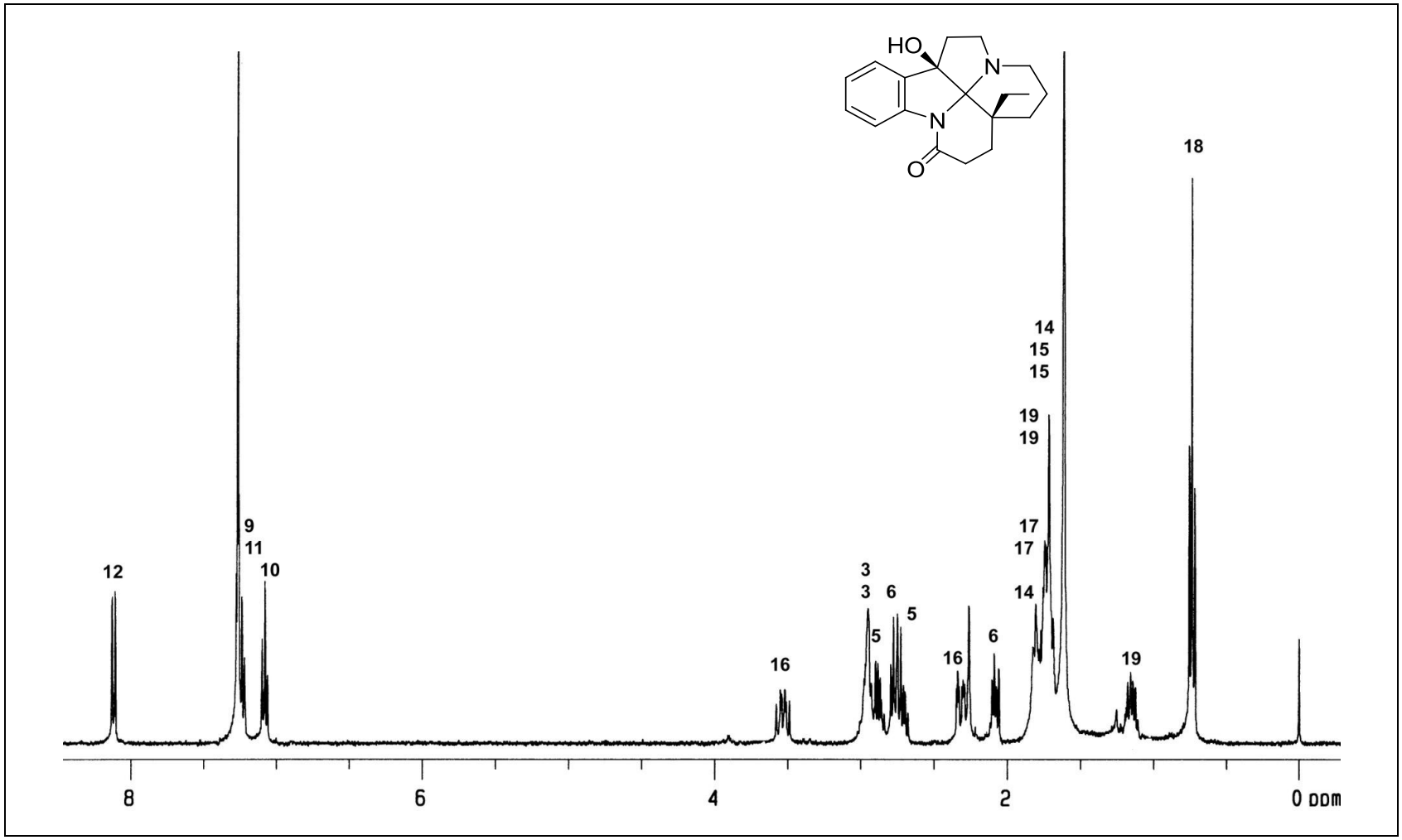
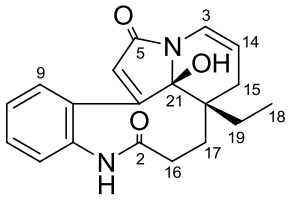


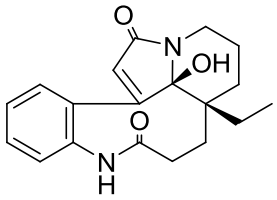
Figure 2.22: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconodine E (**13**)

2.1.3.6 3,14-Dehydroleuconolam (18)

3,14-Dehydroleuconolam (**18**) was obtained in small amounts as a light yellowish oil, with $[\alpha]_D$ −385 ($CHCl_3$, *c* 0.17). The UV spectrum showed absorption maxima at 266 and 323 nm, while the IR spectrum showed bands at 3270, 1694, and 1663 cm^{-1}, corresponding to a hydroxyl group and two lactam carbonyl functions. The EIMS of **18** showed a molecular ion peak at *m/z* 324, and HREIMS measurements established the molecular formula as $C_{19}H_{20}N_2O_3$.



18



19

The NMR data (Table 2.10) of **18** were generally similar to those of leuconolam (**19**),[124,126] except for the absence of the methylene signals at C(3) and the presence instead of two low field methine signals at δ 5.04 (br t, *J* = 6 Hz) and 6.52 (d, *J* = 6 Hz) in the ^{1}H NMR spectrum (Figure 2.24). The ^{13}C NMR data (Table 2.10) of **18** indicated the presence of an additional double bond from the resonances observed at δ 107.6 (δ_H 5.04) and 118.2 (δ_H 6.52), corresponding to two methine carbons. The usual $NCH_2CH_2CH_2$ fragment corresponding to NC(3)–C(14)–C(15) was replaced by a $CH{=}CHCH_2$ fragment in the COSY spectrum, suggesting the site of unsaturation to be at C(3)–C(14), or alternatively, at C(14)–C(15). However, the presence of unsaturation at C(14)–C(15) can be ruled out based on the following observations. The methylene

signals at δ 1.84 and 2.27 were assigned to H(15) based on the observed three-bond correlations from this H(15) to C(17) and C(21), and from H(19) to C(15) in the HMBC spectrum (Figure 2.23). The double bond at C(3)–C(14) is supported by the NMR data ($\delta_{C(3)}$ 118.2, $\delta_{H(3)}$ 6.52; $\delta_{C(14)}$ 107.6, $\delta_{H(14)}$ 5.04) and was further confirmed by the observed three-bond correlations from H(3) to C(15) and C(21). Compound **18** is therefore assigned as 3,14-dehydroleuconolam.

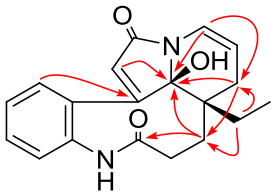


Figure 2.23: Selected HMBCs of **18**

Table 2.10: ^{1}H and ^{13}C NMR Spectroscopic Data of 3,14-Dehydroleuconolam (**18**)[a]

Position	δ_H	δ_C
2	–	179.1
3	6.52 d (6)	118.2
5	–	166.6
6	6.01 s	128.7
7	–	156.4
8	–	133.7
9	7.68 d (7)	129.3
10	7.25 t (7)	127.2
11	7.32 t (7)	130.2
12	7.19 d (7)	127.2
13	–	135.5
14	5.04 br t (6)	107.6
15	1.84 dd (18, 6)	34.5
	2.27 d (18)	
16	1.99 m	28.9
	1.99 m	
17	1.41 m	26.6
	1.41 m	
18	0.50 t (7)	7.4
19	1.11 dq (14, 7)	24.7
	1.46 dq (14, 7)	
20	–	43.6
21	–	92.6
NH	8.48 s	–
OH	4.98 s	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, HMBC, and NOESY/DNOE.

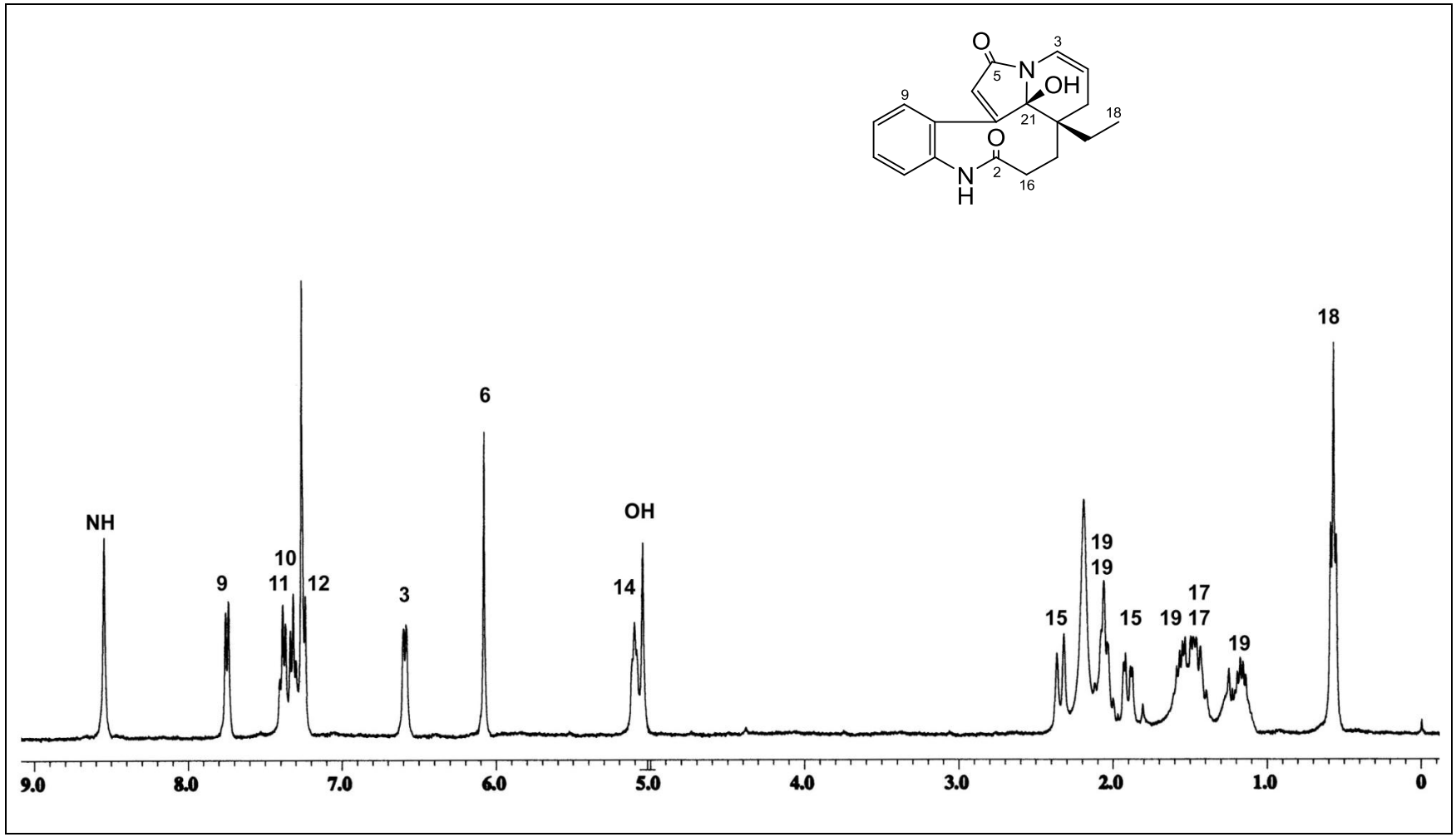
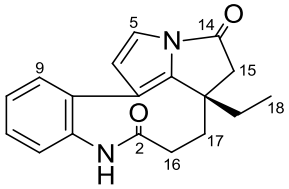


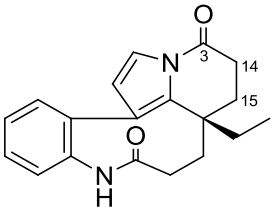
Figure 2.24: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 3,14-dehydroleuconolam (**18**)

2.1.3.7 *Nor*-rhazinicine (22)

Nor-rhazinicine (**22**) was obtained as a light yellowish oil and subsequently crystallized from CH_2Cl_2–MeOH as light yellowish needles, mp 190–192 ^oC, with $[\alpha]_D$ −285 ($CHCl_3$, *c* 0.13). The IR spectrum showed bands due to NH (3252 cm^{-1}) and lactam carbonyl functions (1752 and 1666 cm^{-1}), while the UV spectrum showed absorption maxima at 232 and 273 nm, which is somewhat similar to those of the rhazinilam-type alkaloids.[124,126] The EIMS showed a molecular ion peak at *m/z* 294, and HREIMS measurements established the molecular formula as $C_{18}H_{18}N_2O_2$. The ^{13}C NMR data (Table 2.11) showed a total of eighteen carbon resonances, comprising one methyl, four methylene, six methine, and seven quaternary carbon atoms.



22



27

The NMR data of **22** (Table 2.11) indicated a general similarity to those of rhazinicine (**27**)[188] except for several notable differences. The most prominent difference is the presence of a pair of AB doublets at δ 2.70 and 2.95 (*J* = 18.5 Hz; δ_C 47.8) in the ^1H NMR spectrum (Figure 2.28) of **22**, indicating the presence of an isolated methylene signal. Since the ^{13}C NMR spectrum of **22** indicated the loss of one methylene carbon signal, ring contraction must have occurred either in ring-B (**22a**) or ring-C (**22b**). The two alternative structures **22a** and **22b** are shown in Figure 2.25.

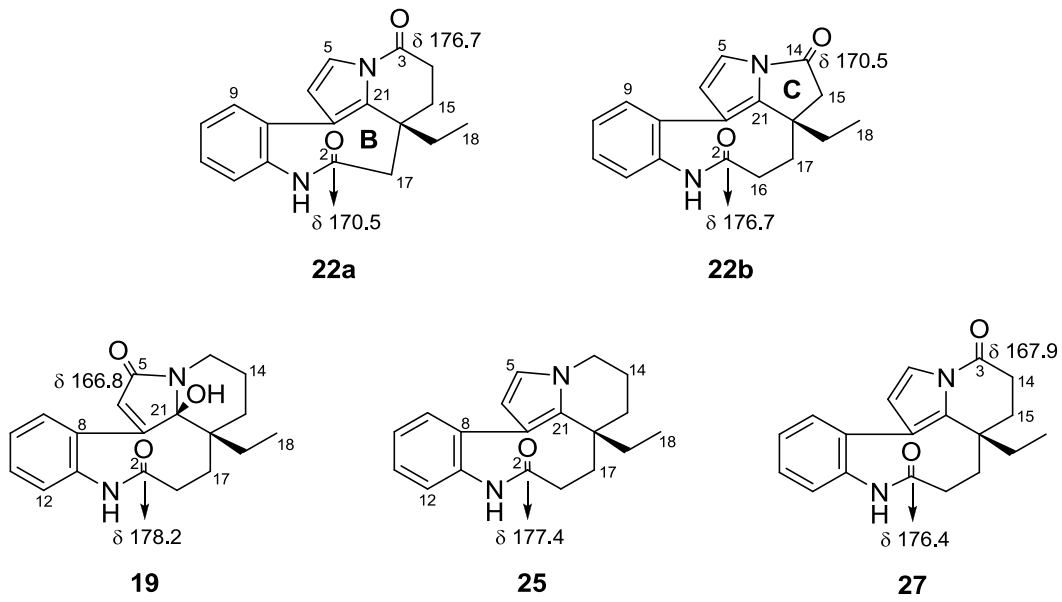
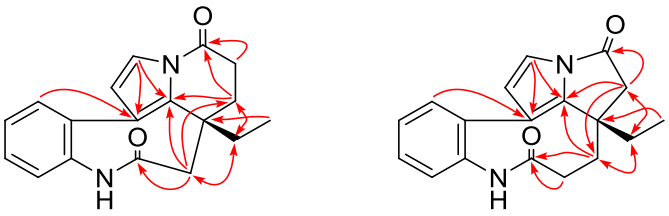


Figure 2.25: Comparison of ^{13}C NMR chemical shifts of C(2) and C(3) (or C(14)) lactam carbonyls in various leuconolam-rhazinilam alkaloids

It transpired that both of the structures proposed (**22a** and **22b**) are in complete accord with the HMBC data (Figure 2.26). Fortunately, the two alternative structures can be distinguished based on consideration of their ^{13}C NMR chemical shifts. In the leuconolam–rhazinilam series of alkaloids (Figure 2.25)[124,126,128] the carbon chemical shift of the C(2) lactam carbonyl with an intact 9-membered ring-B is usually found from δ 176–179 (*e.g.*, $\delta_{C(2)}$ leuconolam 178.2, $\delta_{C(2)}$ rhazinilam 177.4). In the case of rhazinicine, which possesses two lactam carbonyl functions, the resonance of the C(2) lactam carbonyl is observed at $\delta_{C(2)}$176.4, while that of the C(3) lactam carbonyl is found at $\delta_{C(3)}$167.9. In the two possible structures for **22** (**22a**, **22b**), which are consistent with the HMBC data, it can be seen that **22a** incorporates an 8/6 B/C ring, while **22b** incorporates a 9/5 B/C ring. The lactam carbonyl resonances observed for **22** are at δ 176.7 and δ 170.5. The former resonance must be due to a C(2) lactam carbonyl

in an intact 9-membered ring B (while the latter resonance is due to the C(14) lactam carbonyl), which in turn favor structure **22b**.



22a **22b**

Figure 2.26: Selected HMBCs of **22a** and **22b**

Finally, an X-ray diffraction analysis was carried out (Figure 2.27) which confirmed the structure proposed for **22** (or **22b**) based on analysis of the spectroscopic data.

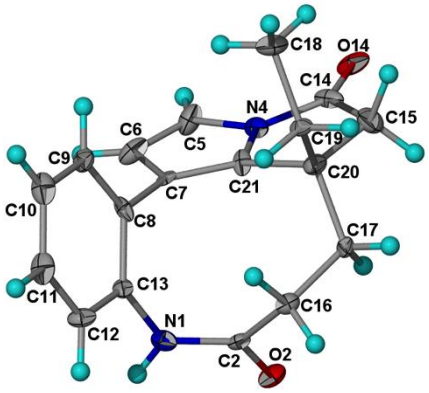
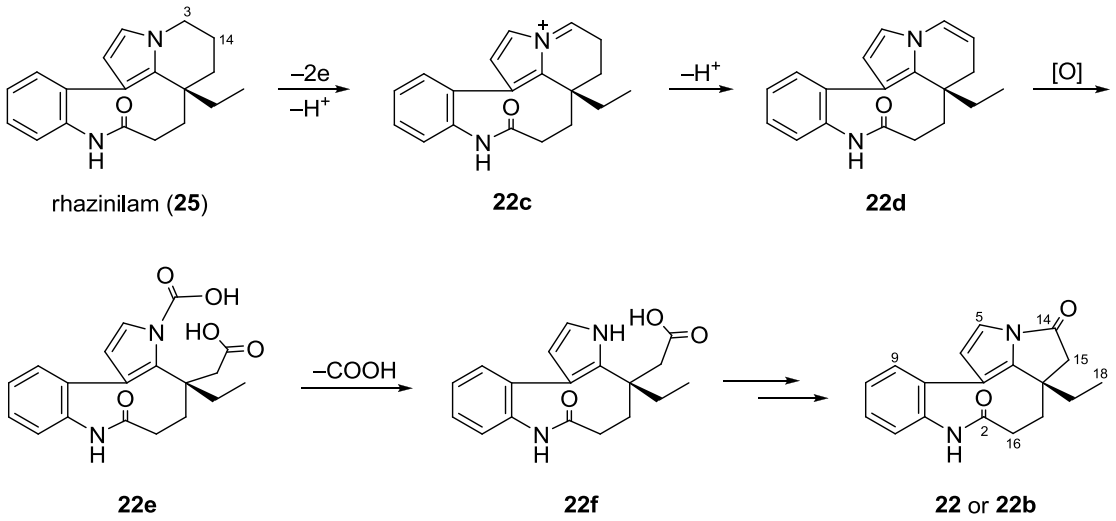


Figure 2.27: X-ray crystal structure of **22**

A possible biogenetic pathway to **22** is as shown in Scheme 2.4. Oxidation of rhazinilam (**25**) leads to the conjugated iminium ion **22c**, which on deprotonation and isomerization, gives the enamine **22d**. Oxidative cleavage of the enamine **22d** yields the dicarboxylic acid derivative **22e**, which on decarboxylation to give the carboxylic acid derivative, **22f**. Esterification of **22f**, followed by ring-closure (lactam formation) gives

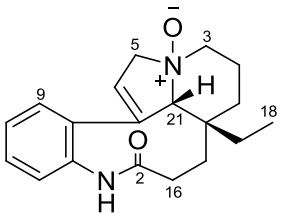
nor-rhazinicine (**22**). Alkaloid **22b** is the first example of a *nor*-rhazinilam alkaloid in the rhazinilam-leuconolam group of alkaloids, in which a carbon atom (C(3), following Scheme 2.4) has been lost from the rhazinilam carbon skeleton.



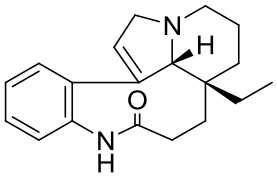
Scheme 2.4: A possible biogenetic pathway to **22**

2.1.3.8 5,21-Dihydrorhazinilam *N*-oxide (23)

5,21-dihydrorhazinilam *N*-oxide (**23**) was isolated as a light yellowish oil, $[\alpha]_D$ −370 ($CHCl_3$, *c* 0.07). The EIMS of **23** showed the highest mass fragment at *m/z* 294 while the molecular ion was detected by ESIMS, which showed an $[M + H]^+$ peak at *m/z* 313 which analyzed for $C_{19}H_{24}N_2O_2$. The UV spectrum showed absorption maxima at 228 and 256 nm, while the IR spectrum showed bands due to NH (3392 cm^{-1}) and lactam carbonyl (1655 cm^{-1}) functions. The NMR spectroscopic data (Table 2.11) of **23** showed a close resemblance to those of 5,21-dihydrorhazinilam (**24**),[124,126] except for the downfield shifts of the C(3), C(5), and C(21) resonances in the ^{13}C NMR spectrum, and the corresponding H(3), H(5), and H(21) resonances in the ^1H NMR spectrum, a behaviour characteristic of alkaloid-*N*-oxides Compound **23** is therefore readily identified as the *N*(4)-oxide of **24**.



23



24

Table 2.11: ^{1}H and ^{13}C NMR Spectroscopic Data of *Nor*-rhazinicine (**22**) and 5,21-Dihydrorhazinilam *N*-oxide (**23**)[a]

Position	**22**		**23**	
	δ_H	δ_C	δ_H	δ_C
2	–	176.7	–	178.5
3	–	–	3.56 td (13, 4) β	66.6
			3.87 br d (13) α	
5	7.00 d (3)	110.7	4.15 dd (15, 3)	73.1
			4.63 d (15)	
6	6.19 d (3)	120.6	5.87 br s	125.8
7	–	117.4	–	137.9
8	–	135.2	–	133.2
9	7.37 dd (7.3, 2)	131.1	7.56 dd (7.5, 2)	128.8
10	7.42 td (7.3, 2)	129.0	7.31 td (7.5, 2)	127.0
11	7.34 td (7.3, 2)	127.6	7.33 td (7.5, 2)	129.4
12	7.27 dd (7.3, 2)	127.4	7.20 dd (7.5, 2)	126.3
13	–	137.0	–	136.4
14	–	170.5	1.81 m	19.1
			1.81 m	
15	2.70 d (18.5)	47.8	1.49 ddd (13, 10, 3)	34.6
	2.95 d (18.5)		1.71 td (13, 3)	
16	2.08 m	28.0	1.46 m	27.8
	2.37 ddd (13, 10, 5)		2.02 br t (13)	
17	2.08 m	37.0	1.82 dd (15, 7)	27.5
	2.26 ddd (13, 10, 5)		2.21 dd (15, 7)	
18	0.72 t (7.3)	8.6	0.67 t (7.5)	7.4
19	1.36 dq (14, 7.3)	28.6	1.22 dq (14, 7.5)	32.4
	1.50 dq (14, 7.3)		1.35 dq (14, 7.5)	
20	–	42.7	–	44.9
21	–	141.4	4.43 s	92.0
NH	7.12 br s	–	8.18 s	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY/DNOE.

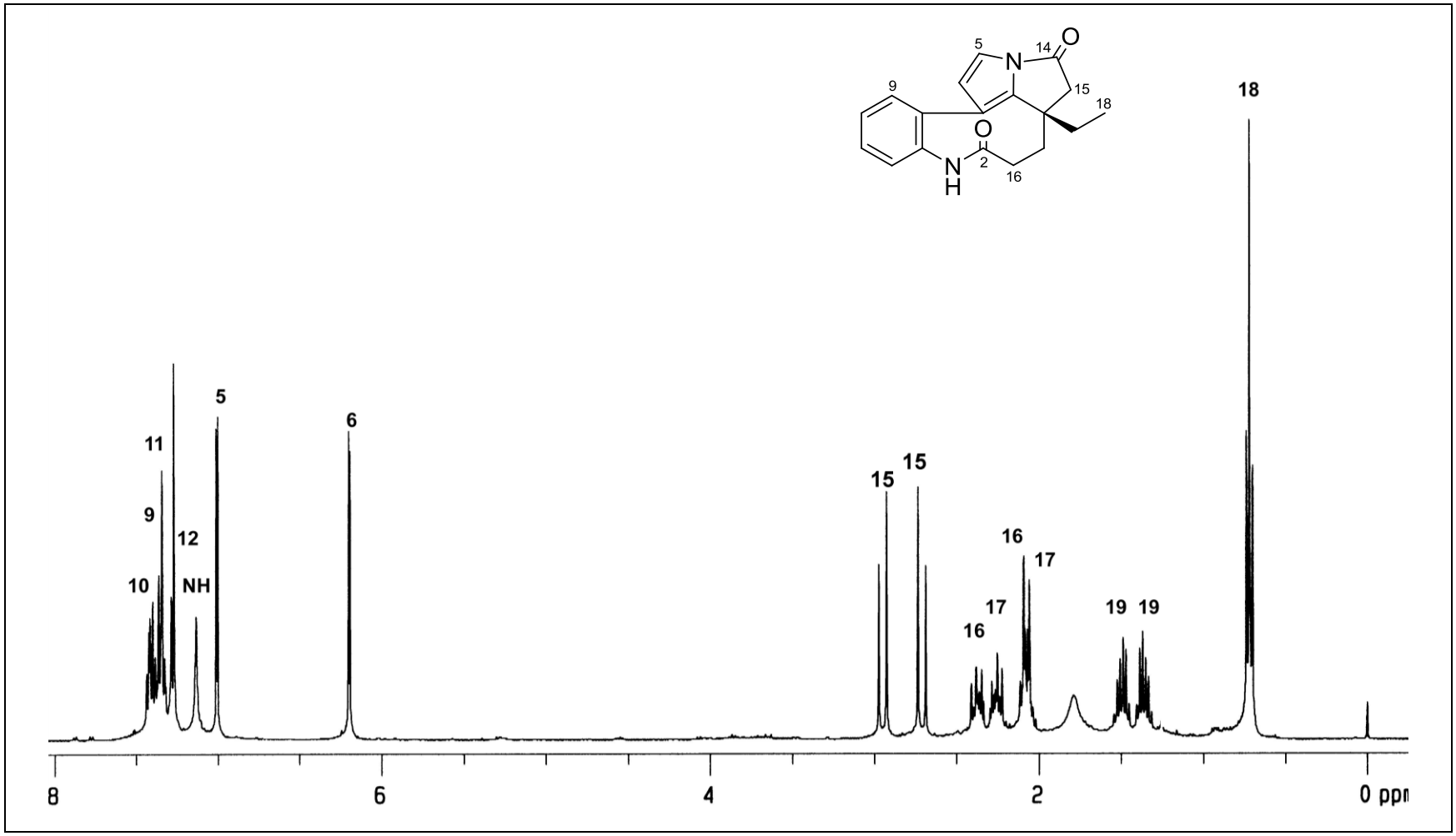


Figure 2.28: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *nor*-rhazinicine (**22**)

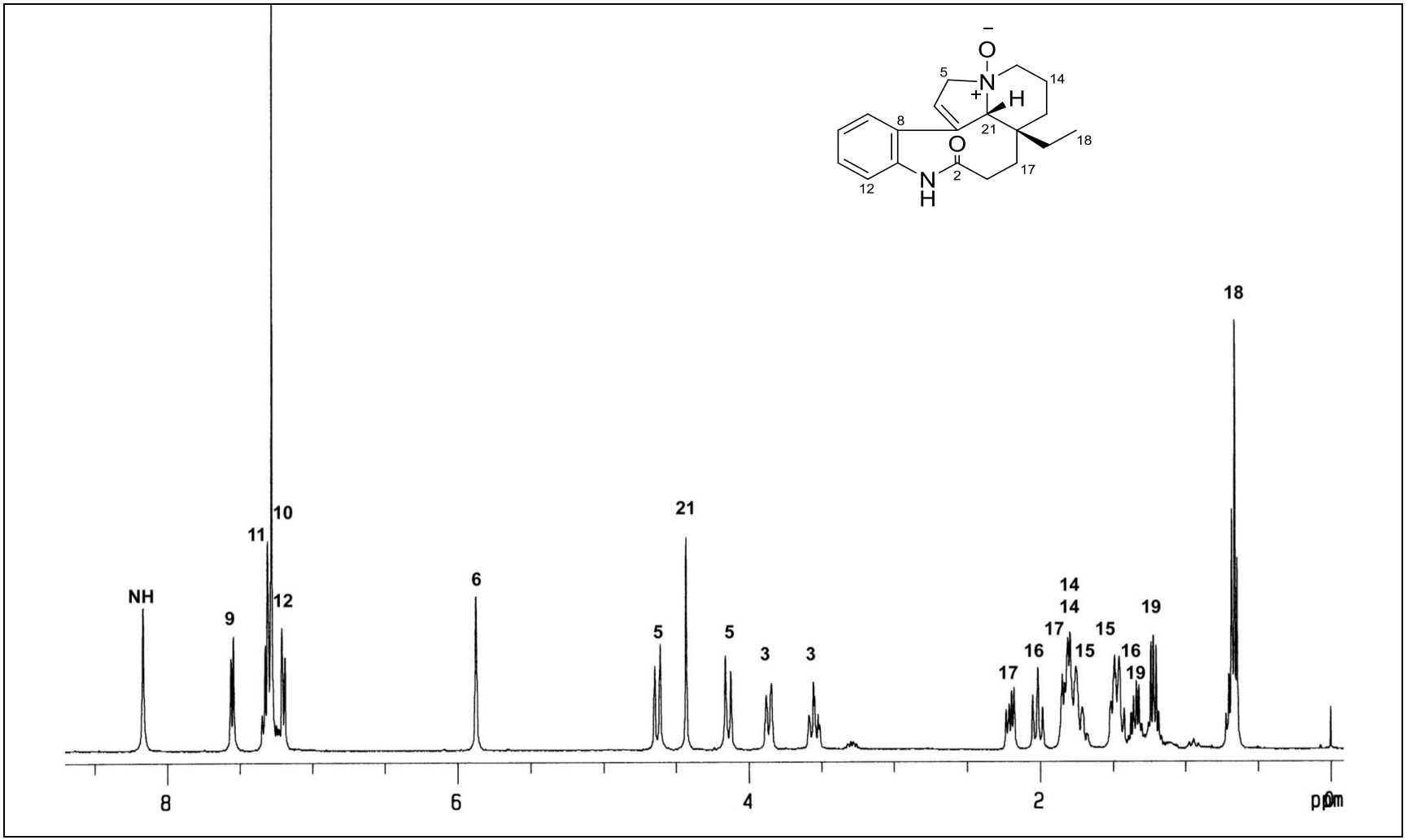


Figure 2.29: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 5,21-dihydrorhazinilam *N*-oxide (**23**)

2.1.3.9 Leuconoxine (14), Leuconodine F (15), Mersicarpine (16), Arboloscine (17), Leuconolam (19), *O*-Methylleuconolam (20), *Epi*-leuconolam (21), 5,21-Dihydrorhazinilam (24), Rhazinilam (25), Rhazinal (26), and Rhazinicine (27)

Eleven known alkaloids belonging to this group, *viz.*, leuconoxine (**14**),[128] leuconodine F (6-oxoleuconoxine) (**15**),[208] mersicarpine (**16**),[159] arboloscine (**17**),[157] leuconolam (**19**),[124,126] *O*-methylleuconolam (**20**),[124,126] *epi*-leuconolam (**21**),[124,126] 5,21-dihydrorhazinilam (**24**),[124,126] rhazinilam (**25**),[124,126] rhazinal (**26**),[230] and rhazinicine (**27**)[188] were also isolated. The ^{1}H NMR spectra of these compounds are shown in Figures 2.30–2.40, while the NMR spectroscopic data are summarized in Tables 2.12–2.17. Other data are given in the Experimental Section.

Table 2.12: ^{1}H NMR Spectroscopic Data of Leuconoxine (**14**), Leuconodine F (**15**), and Mersicarpine (**16**)[a]

H	**14**	**15**	**16**
3	2.73 dd (13, 6.5)	3.10 ddd (13, 11, 4)	3.87 m
	3.96 br d (13)	4.11 ddd (13, 5, 2.3)	3.87 m
6	2.69 d (17)	–	–
	2.87 dd (17, 7.5)		
7	3.82 d (7.5)	4.23 s	–
9	7.17 dd (7, 1)	7.22 dd (7.6, 1)	7.66 br d (8)
10	7.14 td (7, 1)	7.16 td (7.6, 1)	7.09 td (8, 1)
11	7.26 td (7, 1)	7.37 td (7.6, 1)	7.39 td (8, 1)
12	7.77 br d (7)	7.82 dd (7.6, 1)	8.13 br d (8)
14	1.65 m	1.70 m	1.65 m
	1.65 m	1.70 m	1.65 m
15	1.68 m	1.70 m	2.07 m (α)
	1.97 td (13, 4)	2.05 m	1.75 dt (14.3, 3.5) (β)
16	2.49 ddd (19, 6, 1)	2.59 ddd (19, 6, 1.4)	2.48 ddd (18.5, 9.5, 3.5) (α)
	2.80 m	2.86 ddd (19, 14, 6.5)	2.35 ddd (18.5, 8.8, 7.8) (β)
17	1.68 m	1.66 td (14, 6)	1.89 dddd (14, 9.5, 7.8, 1.5) (α)
	1.86 ddd (14, 5, 1)	1.98 ddd (14, 6.5, 1.4)	1.65 m (β)
18	0.93 t (7.4)	0.92 t (7.4)	0.74 t (7.5)
19	1.37 dq (13, 7.4)	1.23 dq (13, 7.4)	1.10 dq (14.5, 7.5)
	1.78 dq (13, 7.4)	1.49 dq (13, 7.4)	1.32 dqd (14.5, 7.5, 1.5)

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

Table 2.13: ^{13}C NMR Spectroscopic Data of Leuconoxine (**14**), Leuconodine F (**15**), and Mersicarpine (**16**)[a]

C	**14**	**15**	**16**
2	172.9	172.2	169.6
3	36.8	37.8	50.5
5	170.8	157.5	–
6	37.6	192.5	–
7	41.9	53.4	168.9
8	135.4	126.2	124.4
9	123.8	125.1	122.2
10	125.5	125.9	124.2
11	128.0	129.9	133.2
12	120.1	121.0	116.7
13	142.1	142.6	146.5
14	20.1	20.1	22.9
15	26.2	26.3	34.3
16	29.4	29.5	29.1
17	26.6	26.6	25.4
18	7.3	7.3	6.8
19	26.9	27.7	21.1
20	38.1	37.6	39.3
21	92.5	88.0	93.8

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

Table 2.14: ^{1}H and ^{13}C NMR Spectroscopic Data of Arboloscine (**17**) and Leuconolam (**19**)[a]

Position	**17**		**19**	
	δ_H	δ_C	δ_H	δ_C
2	–	169.6	–	178.2
3	2.80 m	40.3	2.94 td (12.5, 4.6)	35.6
	3.21 td (12.6, 3.3)		3.98 dd (12.5, 3.5)	
5	–	168.9	–	166.8
6	6.51 s	110.4	5.79 s	128.3
7	–	140.8	–	156.1
8	–	127.1	–	133.5
9	7.43 dd (7.6, 1)	120.4	7.18 dd (7.5, 1)	126.5
10	7.09 td (7.6, 1)	124.0	7.36 td (7.5, 1)	126.9
11	7.33 ddd (8.2, 7.6, 1)	130.9	7.32 td (7.5, 1)	129.7
12	8.35 d (8.2)	118.3	7.90 dd (7.5, 1)	129.6
13	–	142.5	–	135.3
14	1.61 m	26.4	1.48 m	20.0
	1.85 m		1.48 m	
15	2.49 dd (16.9, 9.9)	29.9	1.60 m	24.4
	2.75 m		1.79 td (13.5, 5)	
16	1.43 m	30.3	1.99 td (14, 1.7)	32.4
	1.64 m		2.12 td (14, 7)	
17	1.56 ddd (13, 7, 3)	25.4	1.40 br t (14)	25.7
	2.68 ddd (13, 7, 1)		1.60 m	
18	0.82 t (7.5)	6.95	0.55 t (7.6)	7.3
19	1.48 m	20.1	1.24 dq (13.6, 7.6)	27.9
	1.70 m		1.60 m	
20	–	36.8	–	45.2
21	–	88.1	–	93.8
OH	–	–	5.63 br s	–
NH	–	–	7.84 br s	–
CO_2*Me*	3.83 s	52.3	–	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

Table 2.15: ^{1}H and ^{13}C NMR Spectroscopic Data of *O*-Methylleuconolam (**20**) and *Epi*-leuconolam (**21**) (or 6,7-dehydroleuconoxine (**21a**))[a]

Position	**20**		**21**	
	δ_H	δ_C	δ_H	δ_C
2	–	178.1	–	175.9
3	2.61 td (13, 5)	35.9	3.22 ddd (15, 9.6, 6)	36.8
	4.18 br d (13)		4.46 ddd (15, 12, 4)	
5	–	166.8	–	173.4
6	6.32 s	131.9	6.22 s	118.0
7	–	150.9	–	164.1
8	–	134.5	–	123.4
9	7.27 m	126.8	7.46 ddd (7.5, 1, 0.6)	124.2
10	7.34 m	127.1	7.12 td (7.5, 1)	121.5
11	7.42 m	129.9	7.33 td (7.5, 1)	131.4
12	7.40 m	128.7	8.16 ddd (7.5, 1, 0.6)	115.7
13	–	135.6	–	148.5
14	1.56 m	19.6	1.79 m	16.6
	1.56 m		2.04 m	
15	1.58 m	32.6	1.10 td (14, 7)	25.9
	1.60 m		1.66 ddd (14, 6, 1.5)	
16	2.05 td (14, 1)	27.9	2.62 ddd (15, 5, 2)	34.0
	2.16 dd (14, 6)		3.09 td (15, 6)	
17	1.50 m	26.2	1.71 td (15, 5)	30.3
	1.74 m		2.09 ddd (15, 6, 2)	
18	0.57 t (7.6)	7.3	0.76 t (7.4)	8.2
19	1.28 m	24.2	1.35 dq (13.6, 7.4)	33.0
	1.55 m		1.45 dq (13.6, 7.4)	
20	–	45.5	–	44.4
21	–	97.4	–	93.5
OMe	3.14 s	49.9	–	–
NH	8.16 br s	–	–	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

Table 2.16: ^{1}H and ^{13}C NMR Spectroscopic Data of 5,21-Dihydrorhazinilam (**24**) and Rhazinilam (**25**)[a]

Position	**24**		**25**	
	δ_H	δ_C	δ_H	δ_C
2	–	179.1	–	177.4
3	2.42 td (13, 3)	50.4	3.78 t (13, 5)	46.0
	3.01 br dd (13, 4.5)		4.00 br dd (13, 5.5)	
5	3.23 m	58.1	6.50 d (2.7)	119.5
	3.81 m			
6	5.62 m	130.3	5.75 d (2.7)	109.5
7	–	141.0	–	117.3
8	–	136.0	–	138.0
9	7.22 dd (7.5, 2)	126.8	7.42 dd (7.5, 2)	131.4
10	7.27 m	127.3	7.34 td (7.5, 2)	128.0
11	7.30 td (7.5, 2)	128.1	7.30 td (7.5, 2)	127.2
12	7.22 m	129.4	7.20 dd (7.5, 2)	126.7
13	–	138.7	–	140.3
14	1.36 m	21.2	1.85 m	19.4
	1.77 qt (13, 4.5)		2.22 qdd (13, 5.5, 3)	
15	1.09 td (13, 4.5)	37.2	1.54 dt (13, 3)	33.0
	1.59 br d (13)		1.72 td (13, 3)	
16	1.98 ddd (14, 11.5, 1)	27.8	1.95 dd (12.5, 8)	28.1
	2.15 dd (14, 9.5)		2.37 t (12.5)	
17	1.32 dd (15, 11.5)	26.2	1.47 dd (12.5, 8)	36.6
	2.64 dd (15, 9.5)		2.45 t (12.5)	
18	0.60 t (7.5)	6.9	0.71 t (7.3)	8.1
19	0.86 dq (14.2, 7.5)	29.3	1.24 dq (14.2, 7.3)	30.1
	1.21 dq (14.2, 7.5)		1.46 dq (14.2, 7.3)	
20	–	41.2	–	38.8
21	3.26 s	76.1	–	130.5
NH	7.42 br s	–	6.64 br s	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

Table 2.17: ^{1}H and ^{13}C NMR Spectroscopic Data of Rhazinal (**26**) and Rhazinicine (**27**)[a]

Position	**26**		**27**	
	δ_H	δ_C	δ_H	δ_C
2	–	176.5	–	176.4
3	3.98 ddd (14, 13, 5)	46.3	–	167.9
	4.77 dd (14, 5.5)			
5	–	130.2	7.42 d (3)	116.6
6	6.54 s	125.4	5.93 d (3)	114.6
7	–	120.4	–	121.9
8	–	138.2	–	137.1
9	7.40 dd (7.5, 2)	131.3	7.41 m	130.0
10	7.42 td (7.5, 2)	129.0	7.41 m	128.9
11	7.35 br t (7.5)	127.7	7.37 m	127.8
12	7.26 br d (7.5)	127.3	7.28 d (8)	127.5
13	–	137.6	–	137.1
14	1.95 m	18.5	2.70 ddd (18, 4.5, 3.5)	29.0
	2.19 qdd (13, 5.5, 3)		2.93 ddd (18, 13.5, 5)	
15	1.54 m	31.9	1.73 ddd (13.5, 5, 3.5)	31.7
	1.77 td (13, 3)		2.12 td (13.5, 4.5)	
16	2.04 dd (12.5, 8)	28.0	2.12 m	28.2
	2.43 t (12.5)		2.40 m	
17	1.54 m	36.5	1.58 m	33.6
	2.50 t (12.5)		2.44 m	
18	0.72 t (7.3)	8.1	0.74 t (7.5)	7.9
19	1.26 dq (14.2, 7.3)	29.8	1.31 dq (14.5, 7.5)	29.7
	1.52 dq (14.2, 7.3)		1.47 dq (14.5, 7.5)	
20	–	39.6	–	38.2
21	–	141.3	–	133.2
CHO	9.39 s	178.7	–	–
NH	6.80 s	–	6.75 s	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

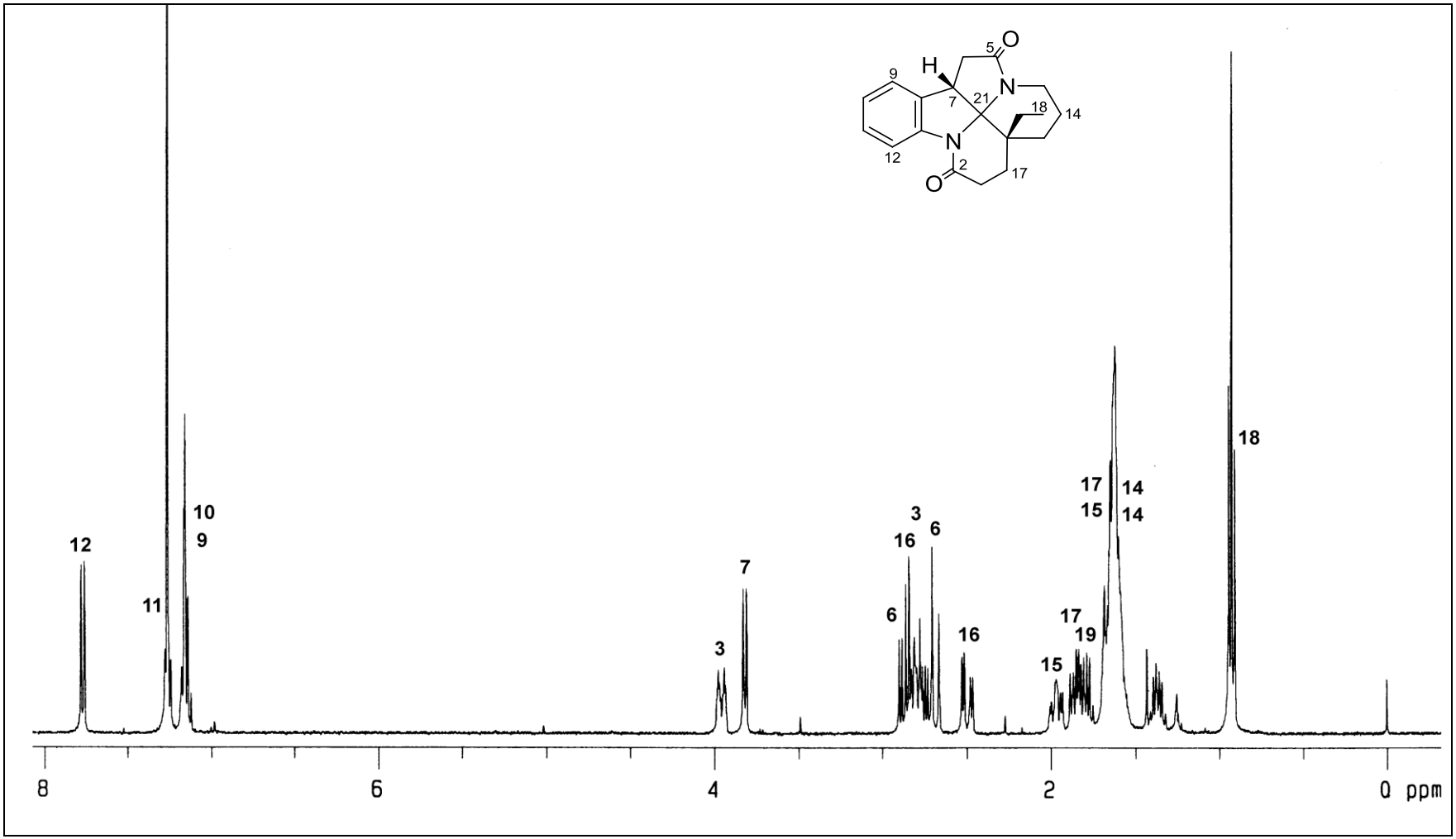


Figure 2.30: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconoxine (**14**)

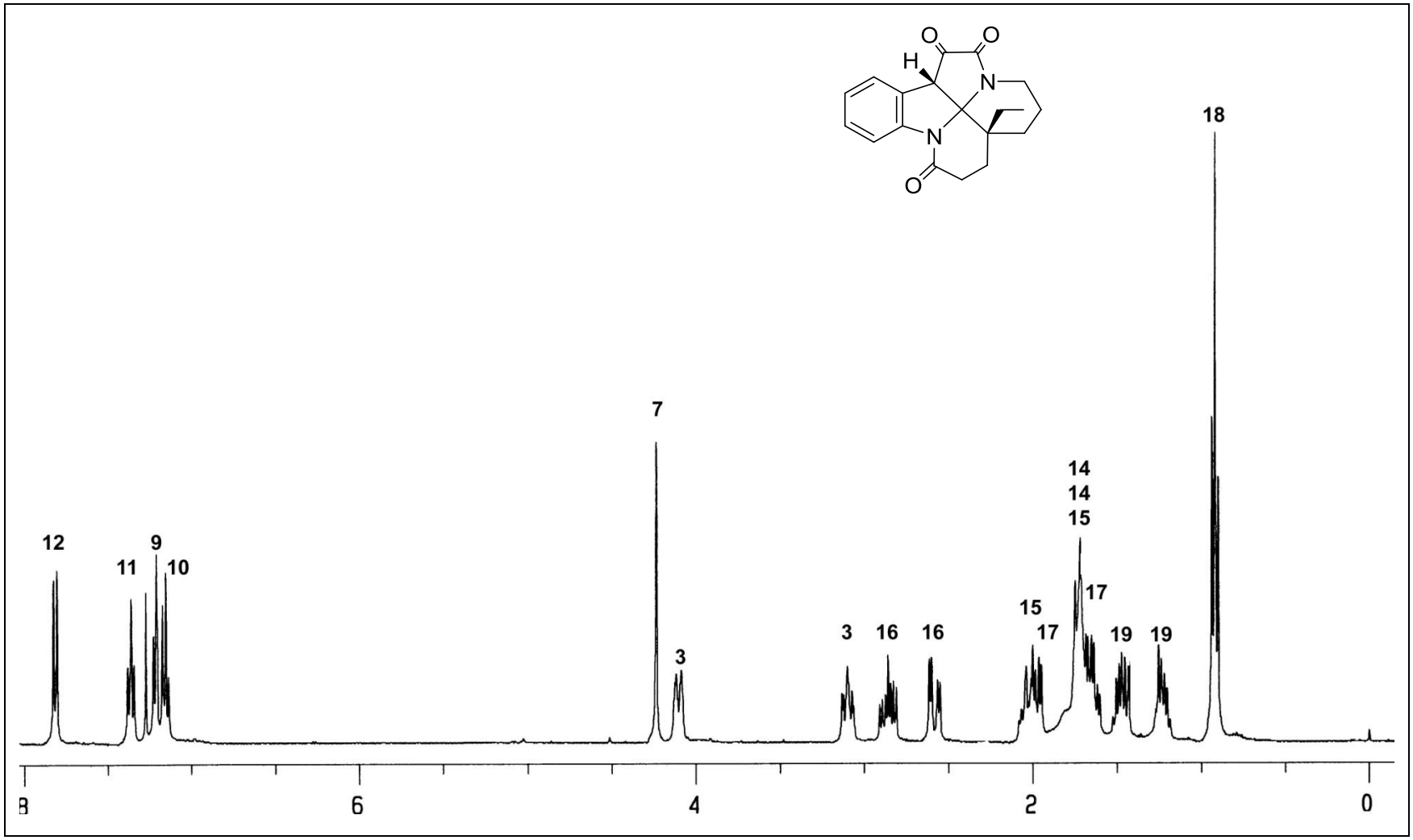


Figure 2.31: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconodine F (**15**)

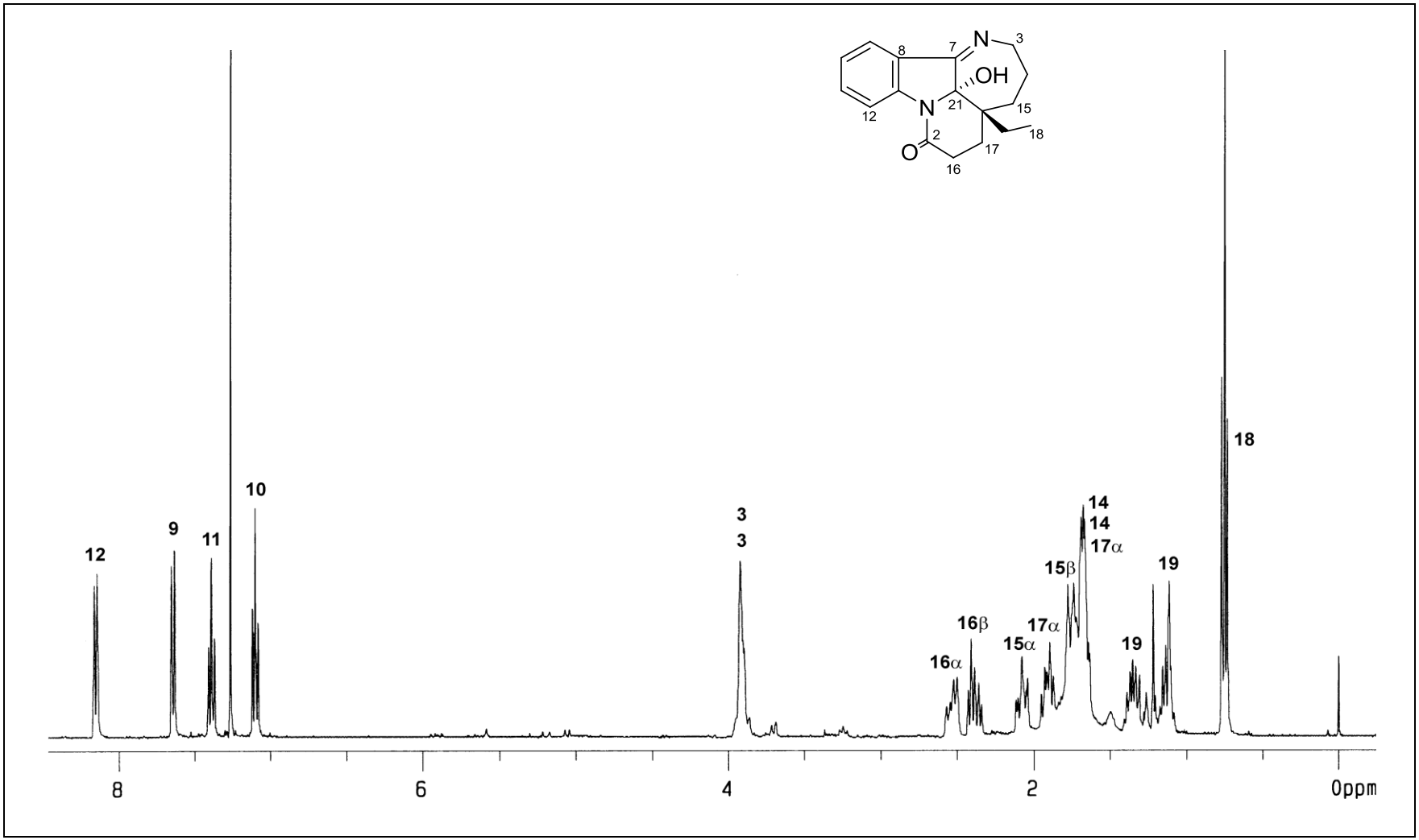


Figure 2.32: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of mersicarpine (**16**)

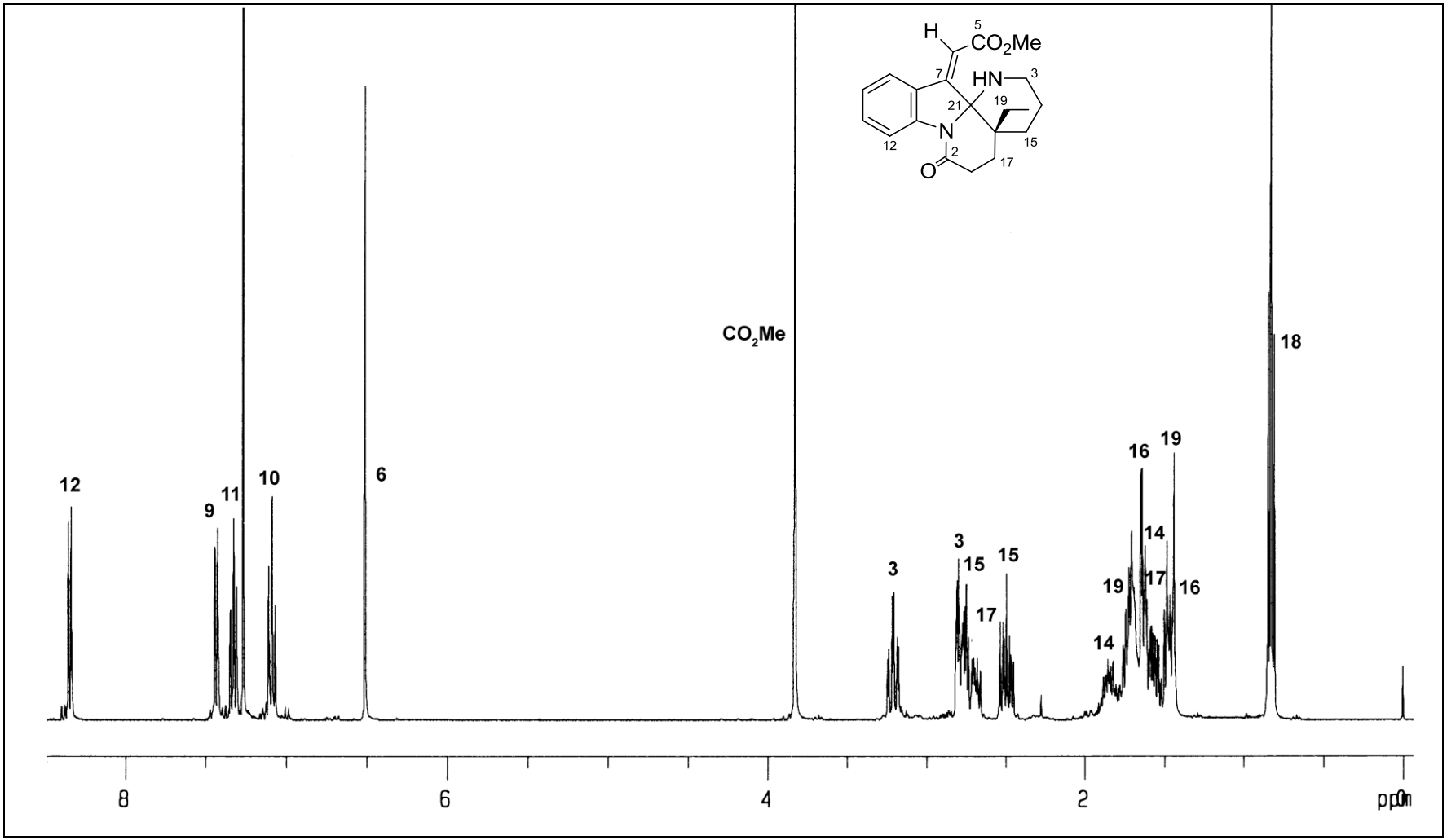


Figure 2.33: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of arboloscine (**17**)

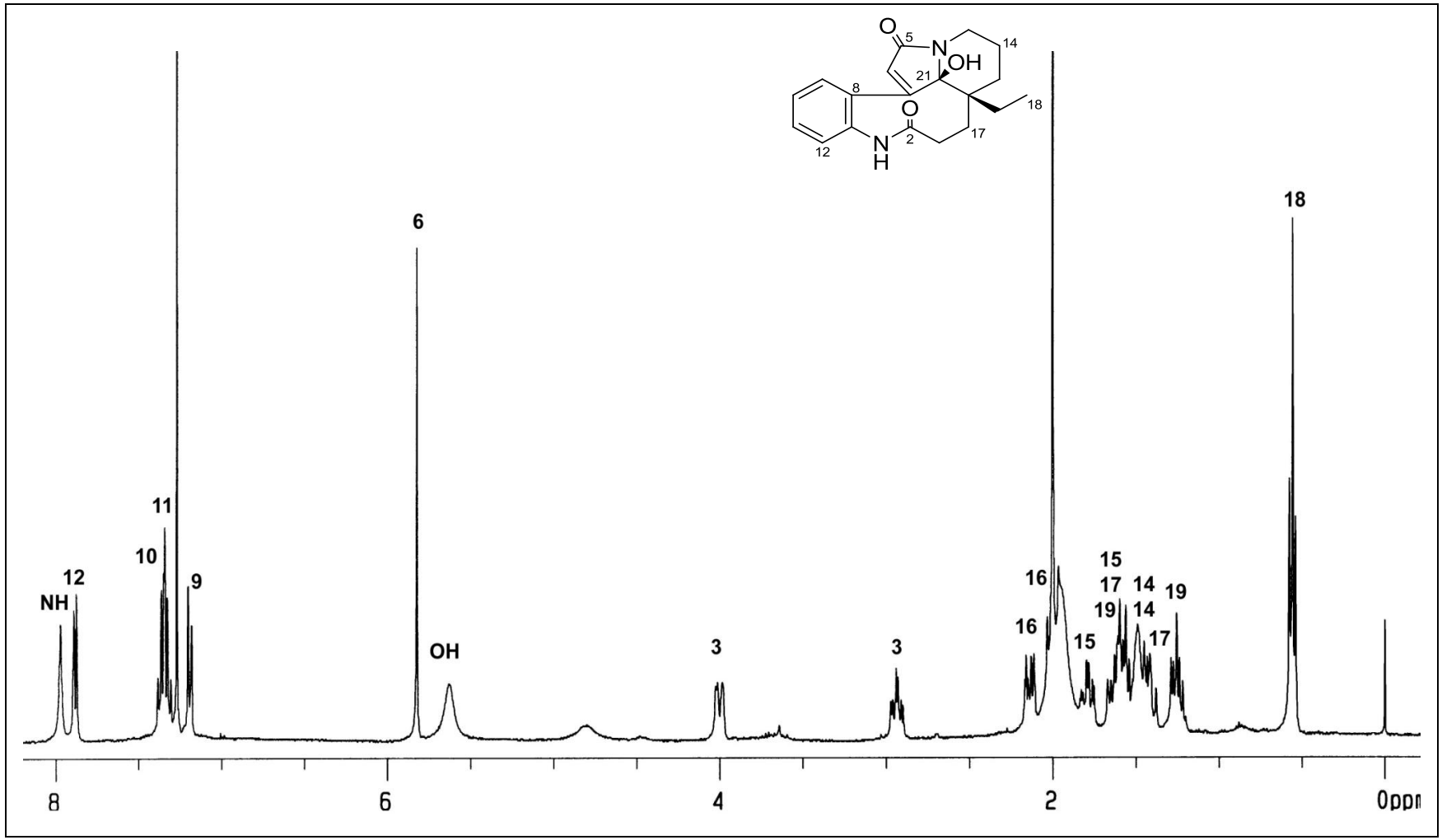


Figure 2.34: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconolam (**19**)

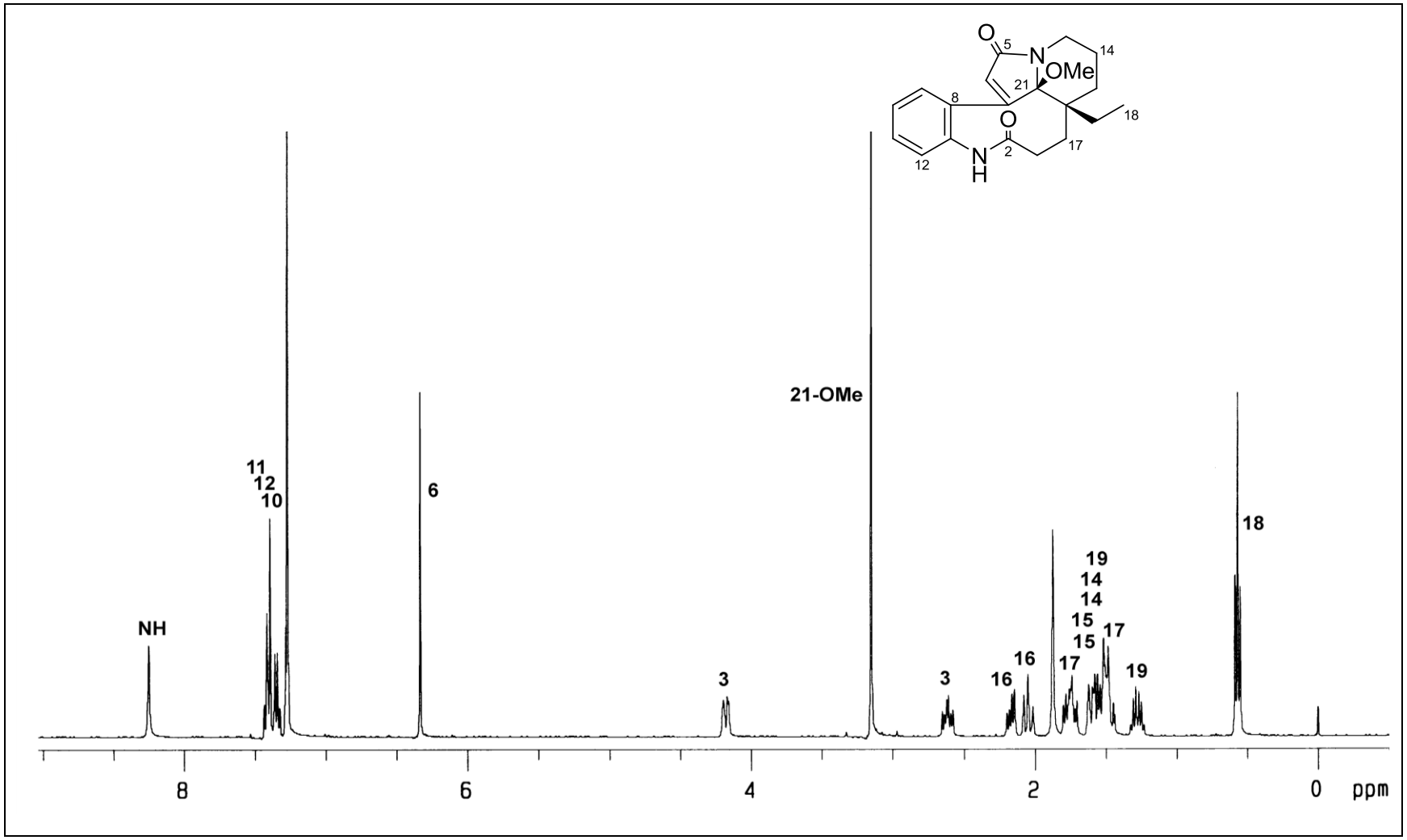


Figure 2.35: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *O*-methylleuconolam (**20**)

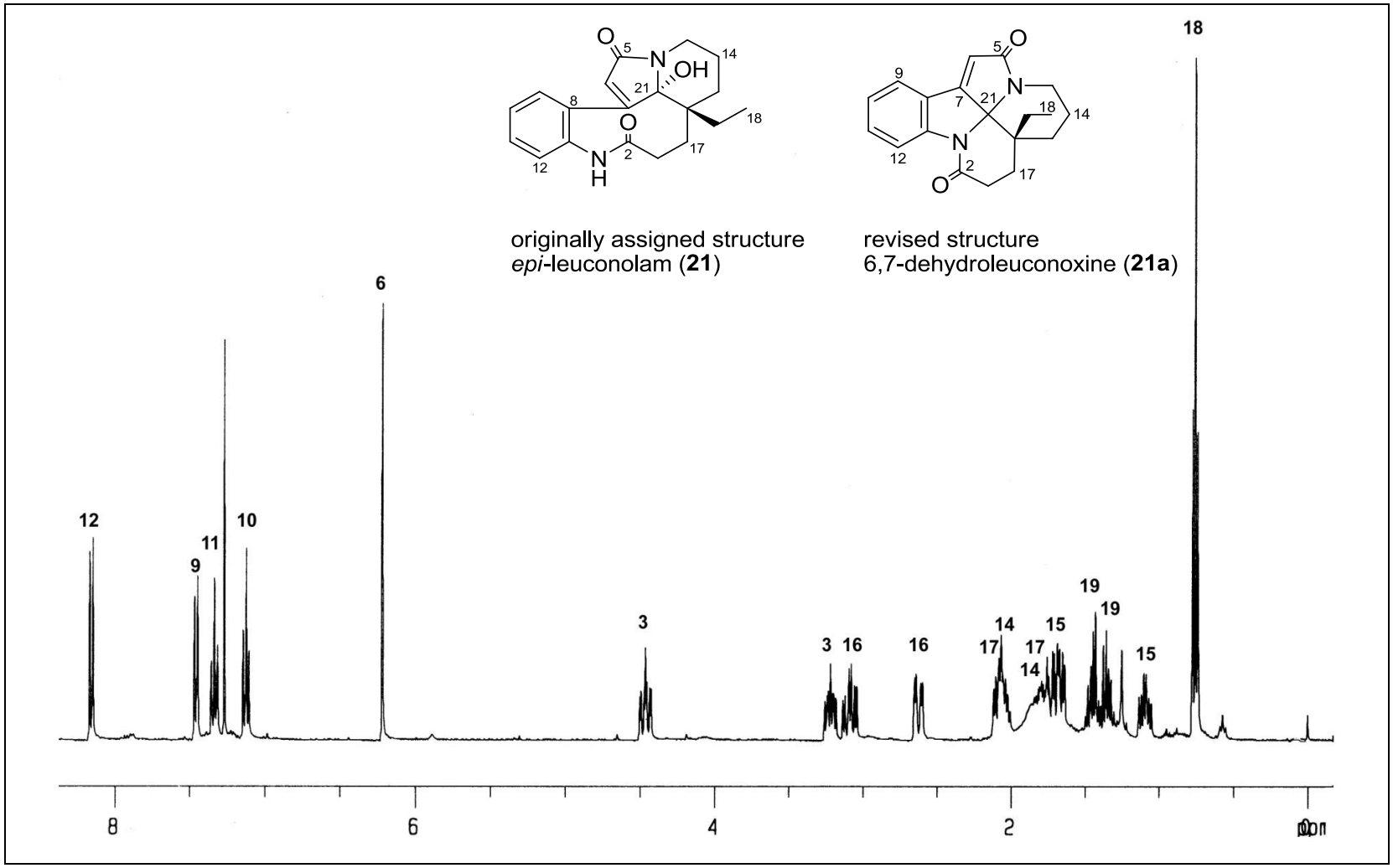
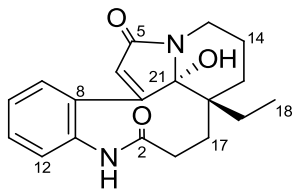


Figure 2.36: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *epi*-leuconolam (**21**) or 6,7-dehydroleuconoxine (**21a**)

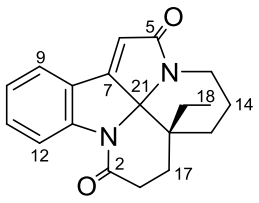
2.1.3.9a Note on *epi*-leuconolam (**21**)

During the preparation of this thesis, concurrent work in this Laboratory by Yun-Yee Low on the chemistry of leuconolam (**19**) indicated that the originally assigned structure for *epi*-leuconolam (**21**) was incorrect.[313] This conclusion was eventually confirmed by X-ray diffraction analysis, which yielded structure **21a** (or 6,7-dehydroleuconoxine) for the previously assigned *epi*-leuconolam (**21**). It was also shown that the '*epi*-leuconolam' (or 6,7-dehydroleuconoxine) was a product formed by transannular cyclization of leuconolam in the presence of acid. It has also been previously shown by Goh *et al*. that '*epi*-leuconolam' is likely an artifact due to the presence of acid, as extraction carried out under neutral or basic conditions did not result in the isolation of this compound, whereas extraction under acidic conditions resulted in its isolation. During the course of this study, an alkaloid corresponding to 6,7-dehydroleuconoxine (**21a**) (NMR data identical to '*epi*-leuconolam' or 6,7-dehydroleuconoxine) was recently reported as a minor alkaloid from the stem-bark extract of *Melodinus* henryi.[314] In view of the above, the possibility that this alkaloid is an artifact due to the action of traces of acid on leuconolam which may have been present, cannot be discounted.[313]



epi-leuconolam

(**21**, originally assigned structure)



6,7-dehydroleuconoxine

(**21a**, revised structure)

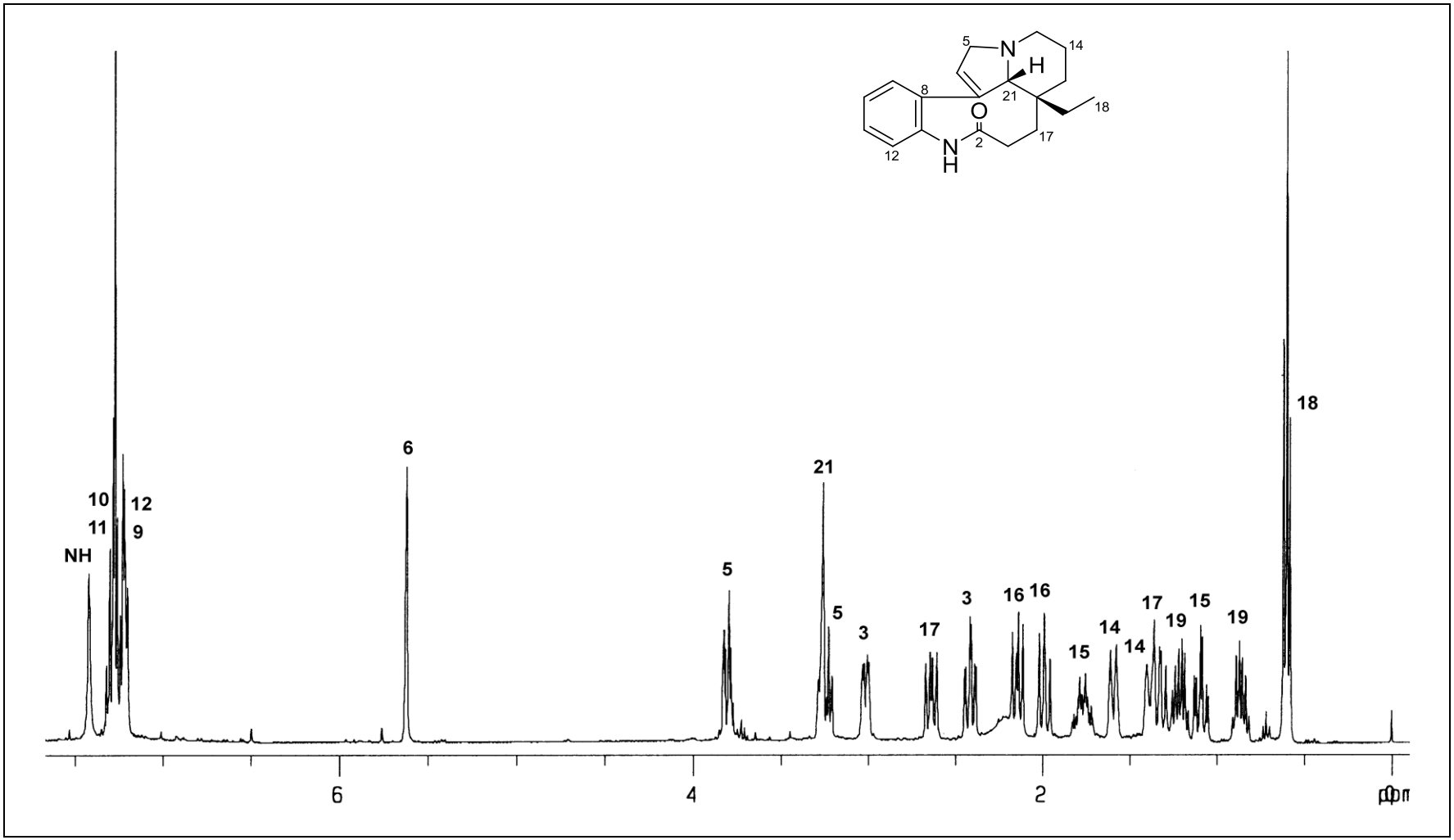


Figure 2.37: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 5,21-dihydrorhazinilam (**24**)

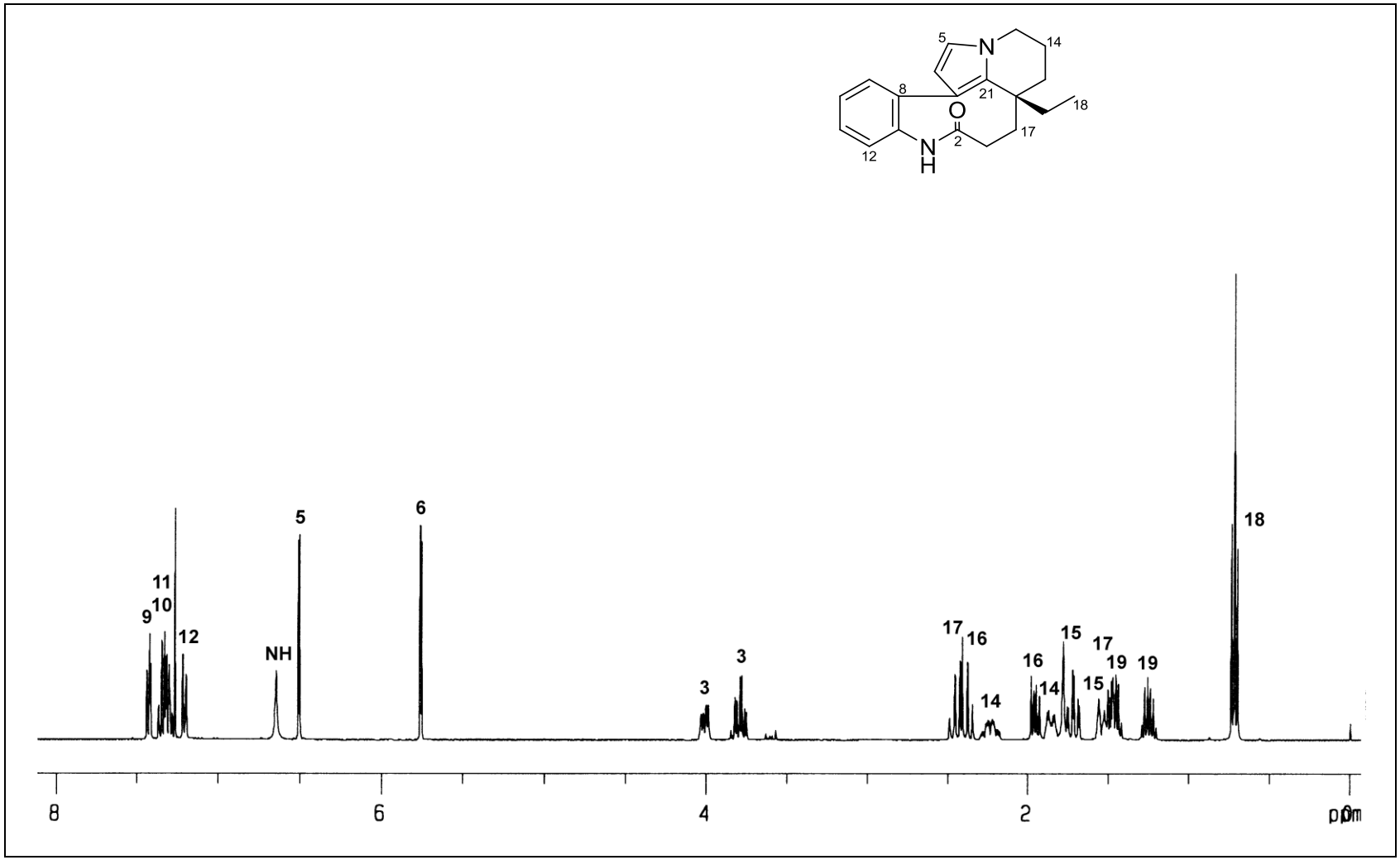


Figure 2.38: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of rhazinilam (**25**)

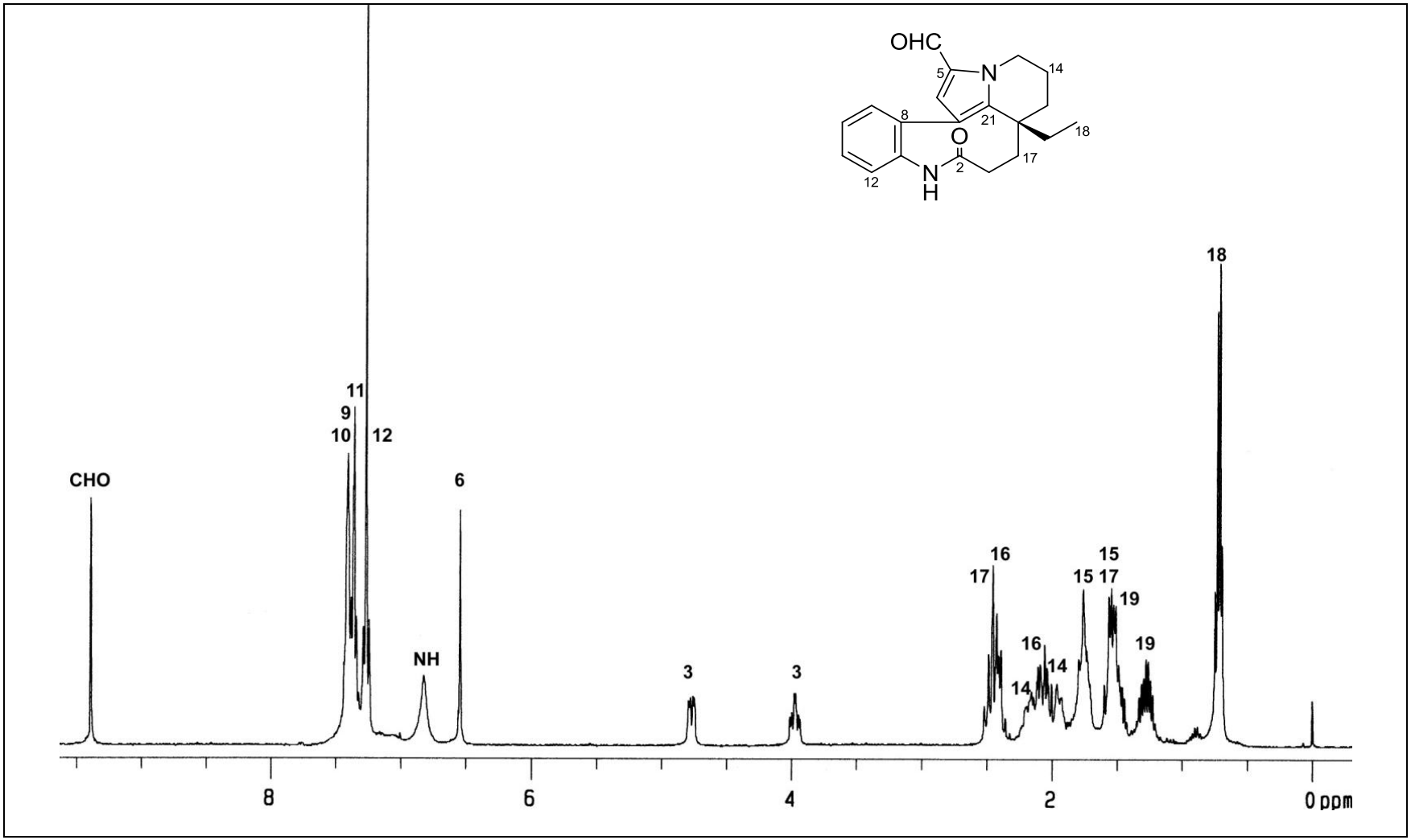


Figure 2.39: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of rhazinal (**26**)

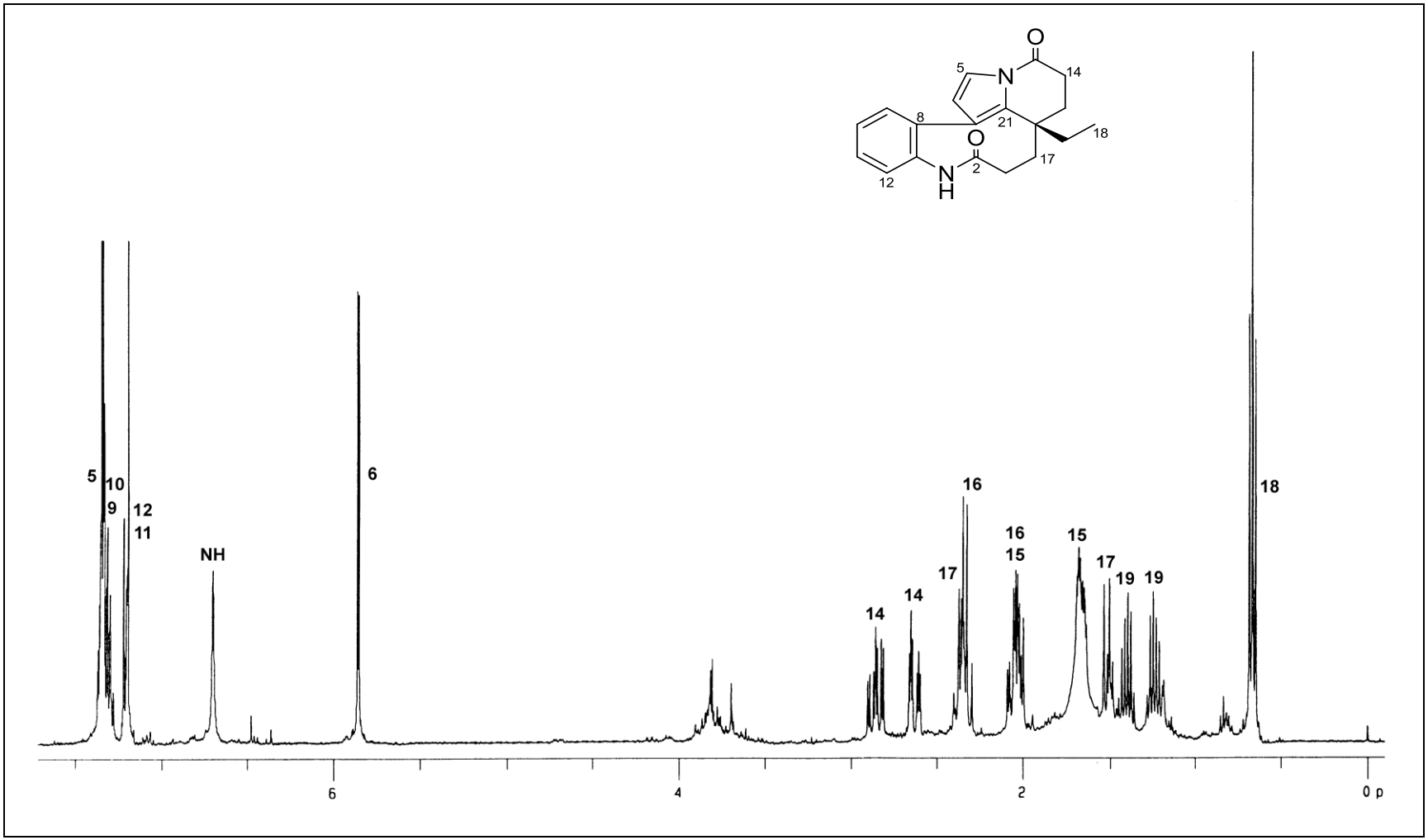
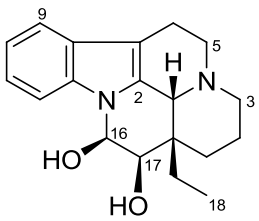


Figure 2.40: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of rhazinicine (**27**)

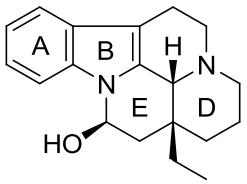
2.1.4 Eburnane Alkaloids

2.1.4.1 (–)-Eburnamaline (28)

(–)-Eburnamaline (**28**)[134] was obtained as a light yellowish oil, with $[\alpha]_D$ –49 ($CHCl_3$, *c* 0.21). The UV spectrum (230 and 280 nm) was typical of an indole chromophore, while the IR spectrum indicated the presence of hydroxyl groups at 3370 cm^{-1}. The EIMS of **28** showed a molecular ion peak at *m/z* 312, which analyzed for $C_{19}H_{24}N_2O_2$ (DBE 9, 16 mass units higher than (–)-eburnamine (**34**)), with a prominent fragment peak due to loss of H_2O at *m/z* 294. The NMR data (Table 2.18) of **28** showed a close resemblance to those of (–)-eburnamine (**34**), except for some notable differences associated with changes involving ring E.



28



34

First, compared with **34**, a doublet was observed at δ 3.90 (δ_C 71.7) which indicated the presence of an oxymethine. This doublet was coupled to the other oxymethine hydrogen, H(16), which required it to be vicinal to C(16). Eburnamaline (**28**) is therefore the 17-hydroxy congener of (–)-eburnamine (**34**). This conclusion is consistent with the loss of the H(17) signals seen in **34** and the presence of a CHCH fragment in **28**, in place of the $CHCH_2$ fragment seen in the COSY spectrum of **34**. Since this eburnane alkaloid co-occurs with (+)-eburnamonine (**29**), (+)-eburnamenine

(**30**), *O*-methylisoeburnamine (**31**), *O*-methyleburnamine (**32**), (+)-isoeburnamine (**33**), and (–)-eburnamine (**34**) found in this plant, and all these alkaloids belong to the 20β, 21β (20*R*, 21*R*) enantiomeric group, it is reasonable to suppose that **28** also belongs to the same series with 20*R*, 21*R* configuration.[150,188,215,315] The configuration at C(16) in the 16-hydroxysubstituted eburnane alkaloids can be deduced from the presence or absence of paramagnetic deshielding exerted by the oxygen of the C(16)-OH substituent.[155,316-318] Thus, in (–)-eburnamine (**34**) (C(16)-βOH), the H(15) resonances are found upfield at *ca.* δ 0.69 and 1.16 (absence of paramagnetic deshielding by OH), whereas in (+)-isoeburnamine (**33**), the α-oriented C(16)-OH causes a downfield shift of the H(15) resonances to δ 1.55 and 1.64, as a result of paramagnetic deshielding by the hydroxyl oxygen.[177,215] The observed upfield resonances for H(15) in eburnamaline (**28**) at δ 0.66 and 1.37, coupled with the observed H(16)/H(15α) NOE (Figure 2.41) provided strong support for the presence of a β-oriented C(16)-OH.

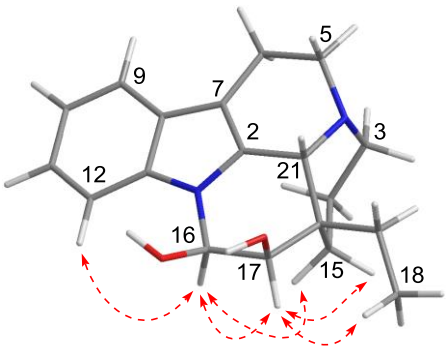
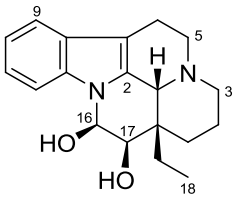


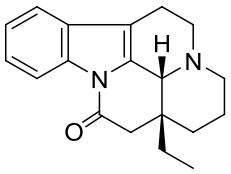
Figure 2.41: Selected NOEs of **28**

The relative configuration at the hydroxy-substituted C(17) was deduced to be *R* (β-OH) based on the following grounds. First, the reciprocal NOEs (Figure 2.41) observed between H(16)/H(17), H(17)/H(15β), and H(17)/H(18) are only consistent with a β-

oriented C(17)-OH. Second, the observed $J_{16\text{-}17}$ of 3 Hz is in agreement of an equatorially-disposed H(17) (an axial or β-oriented H(17) would result in H(17) and H(16) being *trans*-diaxial). Third, the resonances for H(21) and H(19) were shifted downfield (δ 4.02; 1.79, 2.30) when compared to those of (−)-eburnamine (**34**) (δ 3.48; 1.27, 1.89), as a result of paramagnetic deshielding exerted by the proximate oxygen of the β-oriented C(17)-OH.



28



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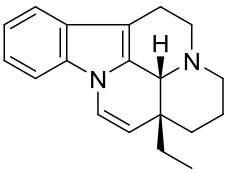

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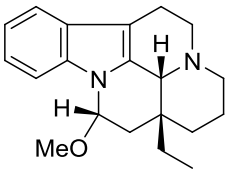

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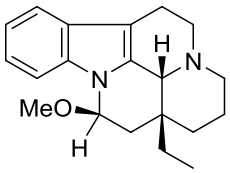
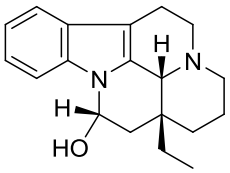
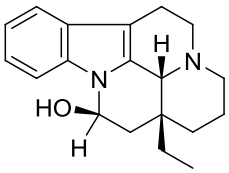


32



33



34

Table 2.18: ^{1}H and ^{13}C NMR Spectroscopic Data of (–)-Eburnamaline (**28**)[a]

Position	δ_H	δ_C
2	–	131.5
3	2.35 m	44.8
	2.53 br d (13)	
5	3.14 ddd (14, 12, 6)	50.9
	3.22 dd (14, 6)	
6	2.42 ddd (16, 6, 2)	16.7
	2.88 dddd (16, 12, 6, 2)	
7	–	105.6
8	–	128.7
9	7.45 dd (7, 1)	118.0
10	7.13 td (7, 1)	120.2
11	7.17 td (7, 1)	121.3
12	7.79 dd (7, 1)	112.3
13	–	137.2
14	1.29 m	20.0
	1.70 dt (13, 3.6)	
15α	0.66 td (13, 3.6)	21.9
15β	1.37 br d (13)	
16	5.54 d (3)	77.0
17	3.90 d (3)	71.7
18	0.89 t (7.7)	6.9
19	1.79 dq (14.5, 7.7)	22.9
	2.30 dq (14.5, 7.7)	
20	–	40.8
21	4.02 br s	55.8

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

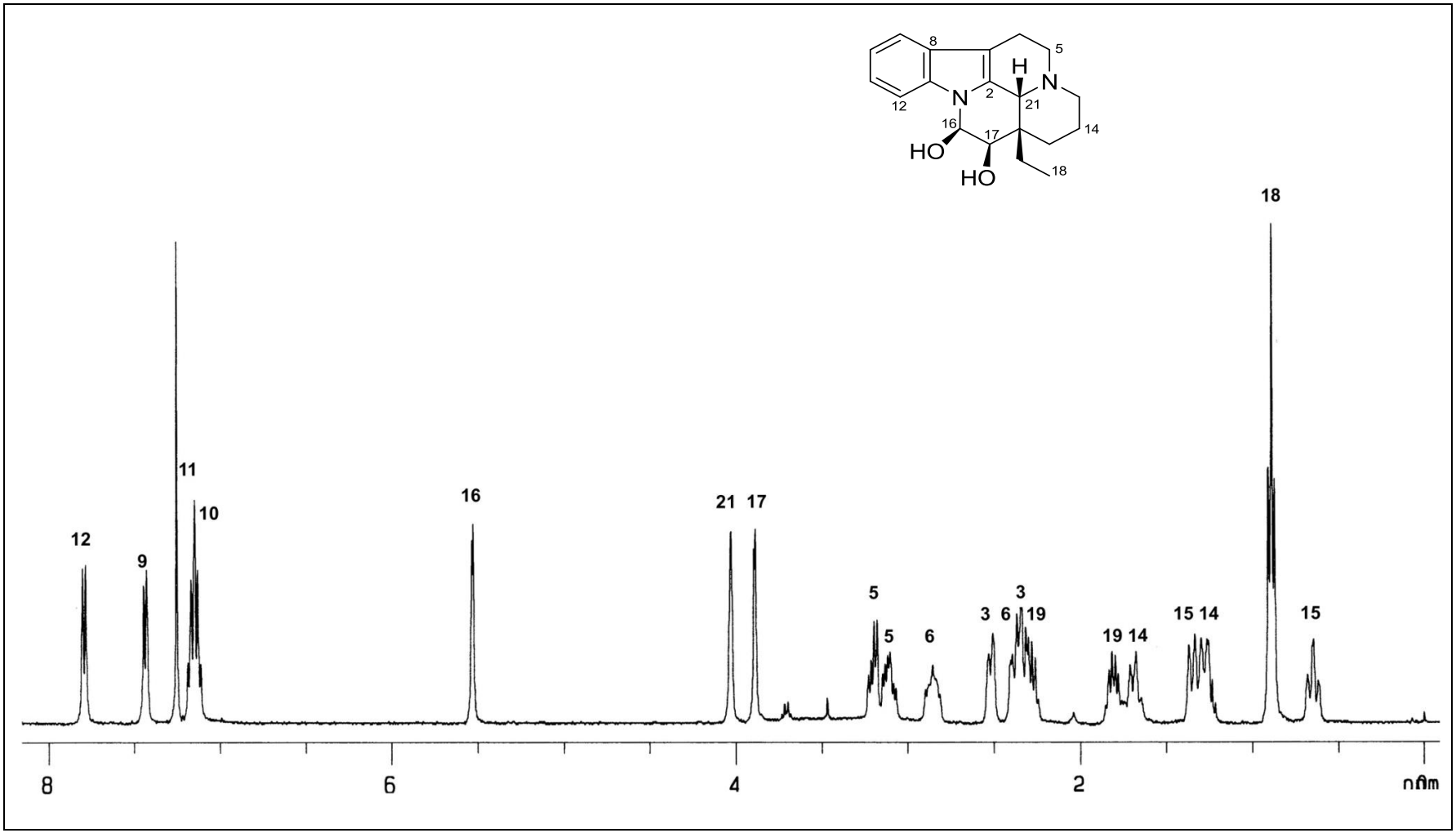


Figure 2.42: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (–)-eburnamaline (**28**)

2.1.4.2 (+)-Eburnamonine (29), (+)-Eburnamenine (30), *O*-Methylisoeburnamine (31), *O*-Methyleburnamine (32), (+)-Isoeburnamine (33), (–)-Eburnamine (34), and (±)-Vincamine (35)

Seven known alkaloids belonging to this group, *viz.*, (+)-eburnamonine (**29**),[214] (+)-eburnamenine (**30**),[211] *O*-methylisoeburnamine (**31**),[124,126,319] *O*-methyleburnamine (**32**),[124,126,319] (+)-isoeburnamine (**33**),[214,215] (–)-eburnamine (**34**),[214] and (±)-vincamine (**35**)[320,321] were also isolated. The ^{1}H NMR spectra of these compounds are shown in Figures 2.43–2.49, while the NMR spectroscopic data are summarized in Tables 2.19–2.23. Other data are given in the Experimental Section.

Table 2.19: ^{1}H NMR Spectroscopic Data of (+)-Eburnamonine (**29**) and (+)-Eburnamenine (**30**)[a]

H	**29**	**30**
3	2.42 ddd (12.5, 11, 4)	2.89 td (13, 3)
	2.59 m	2.96 br s
5	3.24 ddd (14, 11, 6)	3.42 ddd(13, 12, 5.5)
	3.33 br dd (14, 7)	3.54 dd (13, 5.5)
6	2.48 dddd (17, 6, 3, 0.8)	2.77 dd (17.5, 5.5)
	2.90 dddd (17, 11, 7, 3)	3.08 dddd (17.5, 12, 5.5, 3)
9	7.43 dd (7, 1.5)	7.48 br d (8)
10	7.30 td (7, 1.5)	7.14 td (8, 1)
11	7.32 td (7, 1.5)	7.24 td (8,1)
12	8.37 dd (7, 1.5)	7.36 br d (8)
14	1.39 m	1.55 m
	1.76 m	1.97 m
15	1.03 td (13.5, 4)	1.21 td (13, 3)
	1.49 dt (13.5, 4)	1.55 m
16	–	6.96 d (7.8)
17	2.58 d (16.7)	5.12 d (7.8)
	2.67 d (16.7)	
18	0.93 t (7.5)	1.04 t (7.4)
19	1.66 dq (14, 7.5)	1.85 dq (14, 7.4)
	2.05 dq (14, 7.5)	2.12 dq (14, 7.4)
21	3.98 br s	4.50 s

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

Table 2.20: ^{13}C NMR Spectroscopic Data of (+)-Eburnamonine (**29**) and (+)-Eburnamenine (**30**)[a]

C	**29**	**30**
2	132.0	127.7
3	44.2	45.4
5	50.5	52.4
6	16.4	16.5
7	112.4	106.8
8	130.0	127.4
9	117.9	118.8
10	123.7	120.7
11	124.2	122.7
12	116.1	109.0
13	134.0	134.2
14	20.5	19.8
15	26.8	30.3
16	167.5	120.3
17	44.1	116.2
18	7.6	9.0
19	28.2	27.7
20	38.2	37.8
21	57.4	56.6

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

Table 2.21: ^{1}H and ^{13}C NMR Spectroscopic Data of *O*-Methylisoeburnamine (**31**) and *O*-Methyleburnamine (**32**)[a]

Position	**31**		**32**	
	δ_H	δ_C	δ_H	δ_C
2	–	131.2	–	136.7
3	2.59 m	44.9	2.34 td (13, 3)	44.4
	2.59 m		2.51 m	
5	3.25 td (13.6, 5.4)	51.4	2.27 m	50.9
	3.33 dd (13.6, 6.8)		2.27 m	
6	2.55 m	16.9	2.54 m	16.9
	2.97 dddd (16, 11, 6.8, 2.3)		2.95 dddd (16, 11, 6.8, 2.3)	
7	–	105.5	–	105.9
8	–	128.8	–	128.7
9	7.46 br d (7.7)	118.3	7.47 dd (7, 1)	118.1
10	7.11 td (7.7, 1)	120.1	7.14 td (7, 1)	120.2
11	7.16 td (7.7, 1)	121.2	7.18 td (7, 1)	121.5
12	7.26 br d (7.7)	110.6	7.58 dd (7, 1)	112.0
13	–	134.7	–	133.2
14	1.35 m	20.9	1.28 m	20.6
	1.74 m		1.72 dt (13, 4)	
15	1.39 m	25.6	0.88 td (13, 4)	25.4
	1.80 m		1.38 m	
16	5.46 dd (4, 1.3)	83.1	5.53 dd (9.5, 5)	82.4
17	1.79 dd (15, 4)	35.0	1.84 dd (14, 9.5)	36.7
	2.25 br d (15)		2.15 dd (14, 5.5)	
18	0.93 t (7.5)	7.8	0.93 t (7.5)	7.7
19	1.49 dq (14, 7.5)	29.1	1.58 dq (14, 7.5)	29.0
	2.13 dq (14, 7.5)		2.10 dq (14, 7.5)	
20	–	34.7	–	36.7
21	3.87 s	59.3	3.91 s	58.9
OMe	3.50 s	55.8	3.33 s	50.7

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

Table 2.22: ^{1}H NMR Spectroscopic Data of (+)-Isoeburnamine (**33**), (−)-Eburnamine (**34**), and (±)-Vincamine (**35**)[a]

H	**33**	**34**	**35**
3	2.59 td (13, 3)	2.29 td (13, 2.9)	2.51 td (11, 2.9)
	2.66 br d (13)	2.51 m	2.60 dd (11, 2.9)
5	3.25 ddd (13.6, 11.5, 5.5)	3.17 ddd (13.5, 11.5, 5.8)	3.27 ddd (14, 11, 6)
	3.33 dd (13.6, 6.5)	3.24 dd (13.5, 6.5)	3.33 dd (14, 7)
6	2.54 ddd (16, 5.5, 1.5)	2.51 m	2.54 m
	2.91 dddd	2.92 dddd	2.99 dddd
	(16, 11.5, 6.5, 2.5)	(16, 11.5, 6.5, 2)	(16.6, 11, 7, 2)
9	7.50 br d (7.5)	7.47 ddd (7, 1.5, 0.8)	7.49 m
10	7.15 td (7.5, 1.5)	7.16 td (7, 1.5)	7.11 m
11	7.20 td (7.5, 1.5)	7.19 td (7, 1.5)	7.12 m
12	7.41 br d (7.5)	7.73 ddd (7, 1.5, 0.8)	7.09 m
14	1.39 dt (13, 3)	1.26 m	1.37 m
	1.76 qt (13, 3)	1.68 qt (13, 3.5)	1.68 m
15	1.55 dt (13, 3)	0.82 td (13, 3.5)	1.42 m
	1.64 td (13, 3)	1.34 m	1.73 m
16	6.06 dd (4.8, 1)	5.55 dd (9.5, 5)	–
17	2.00 dd (15, 4.8)	1.48 dd (13.8, 9.5)	2.12 d (14)
	2.19 br d (15)	2.29 dd (13.8, 9.5)	2.22 d (14)
18	0.93 t (7.6)	0.88 t (7.6)	0.91 t (7.6)
19	1.46 dq (14.5, 7.6)	1.42 dq (14.4, 7.6)	1.47 dq (14, 7.6)
	2.19 dq (14.5, 7.6)	2.04 dq (14.4, 7.6)	2.24 dq (14, 7.6)
21	3.85 br s	3.71 br s	3.92 s
OH	–	–	4.60 br s
OMe	–	–	3.82 s

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

Table 2.23: ^{13}C NMR Spectroscopic Data of (+)-Isoeburnamine (**33**), (−)-Eburnamine (**34**), and (±)-Vincamine (**35**)[a]

C	**33**	**34**	**35**
2	131.2	132.4	131.2
3	44.9	44.2	44.4
5	51.3	50.5	51.0
6	16.7	16.7	16.8
7	105.6	105.1	105.9
8	129.0	128.6	128.9
9	118.5	117.9	118.5
10	120.1	120.0	121.7
11	121.2	121.1	120.3
12	109.7	112.3	110.3
13	134.7	136.7	134.1
14	21.0	20.2	20.7
15	26.6	24.6	25.1
16	74.7	76.6	81.9
17	39.9	43.0	44.6
18	7.6	7.5	7.6
19	29.0	28.4	28.9
20	34.6	36.7	35.1
21	59.2	58.4	59.1
CO_2*Me*	–	–	54.3
CO_2Me	–	–	174.4

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

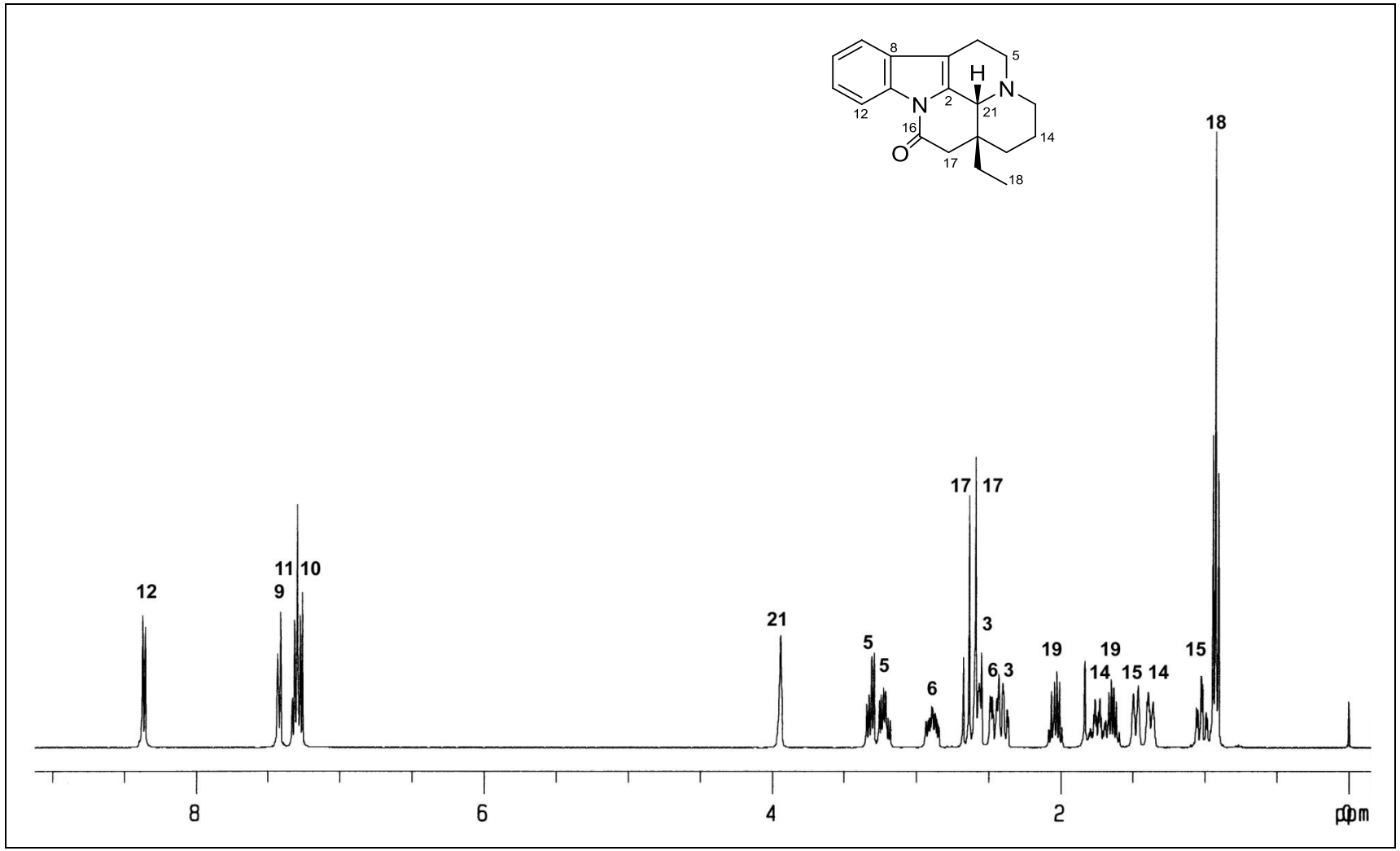


Figure 2.43: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (+)-eburnamonine (**29**)

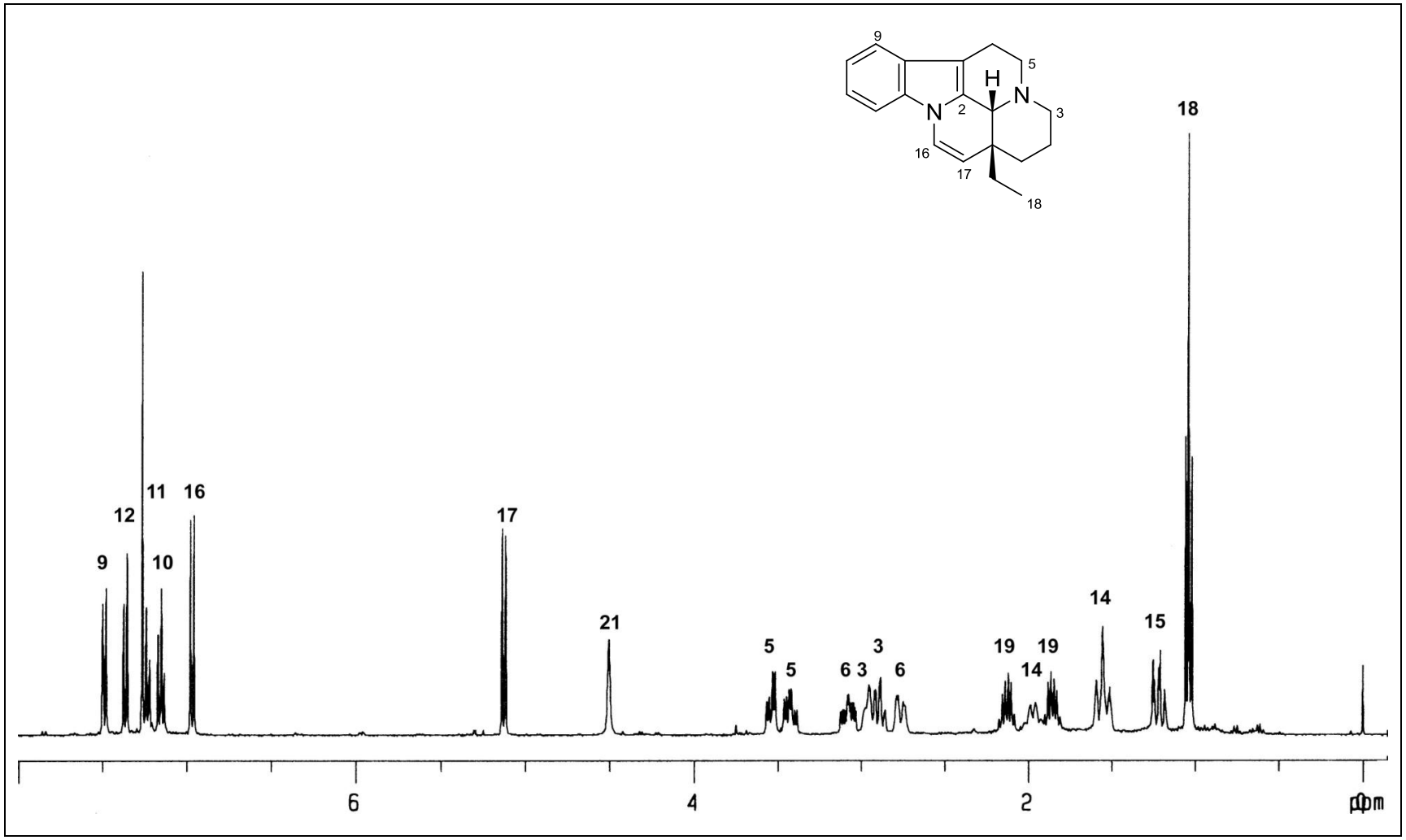


Figure 2.44: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (+)-eburnamenine (**30**)

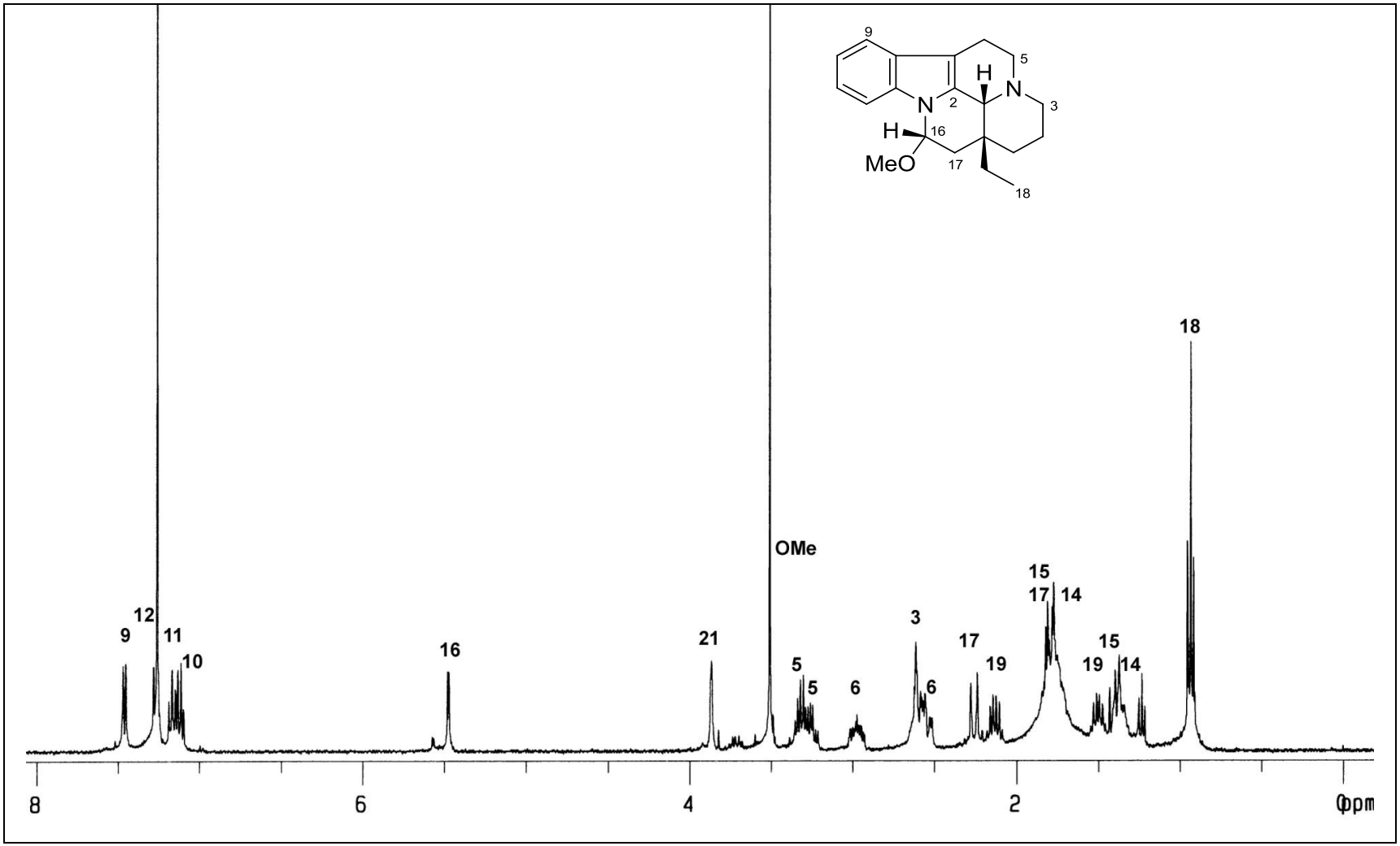


Figure 2.45: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *O*-methylisoeburnamine (**31**)

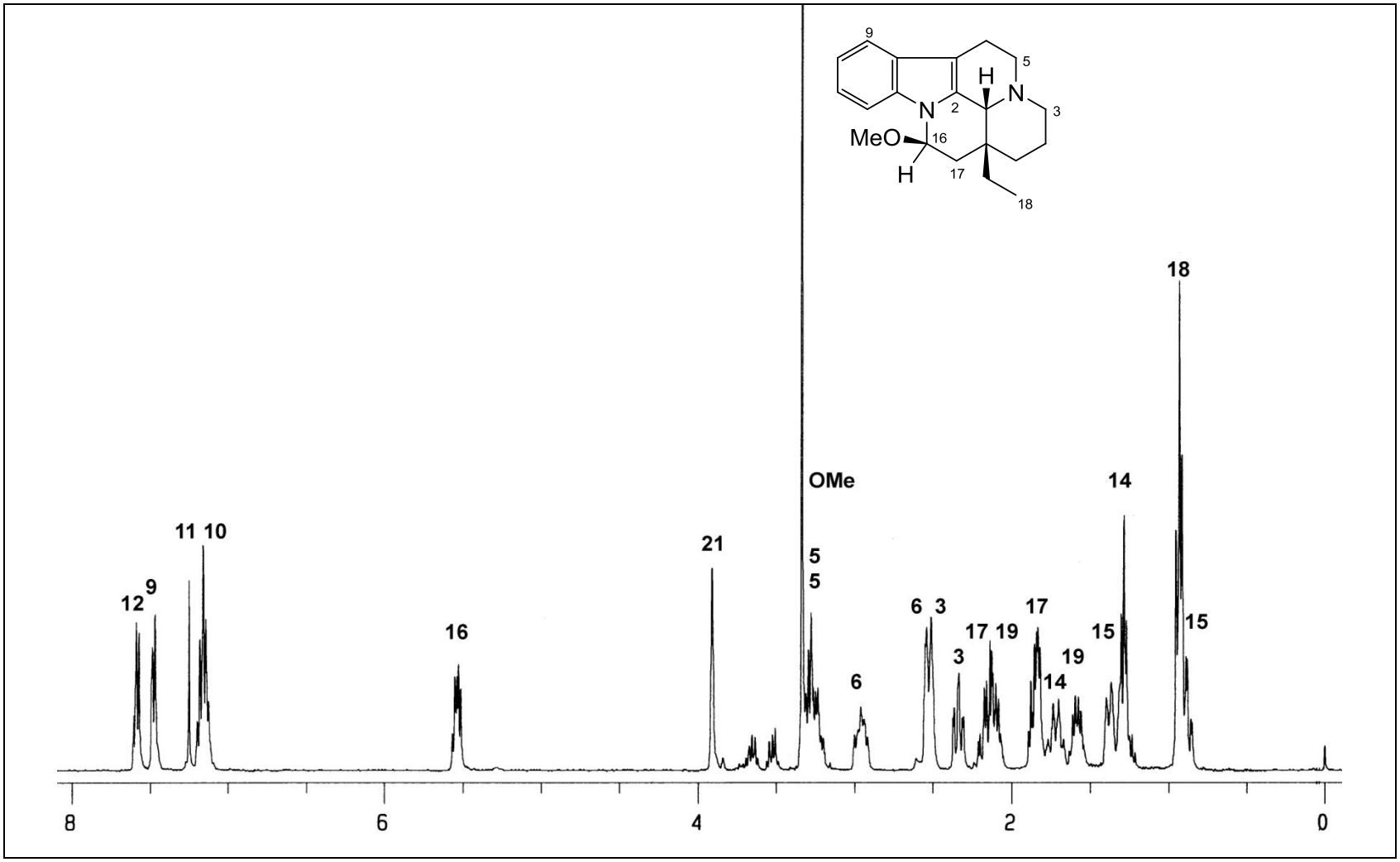


Figure 2.46: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *O*-methyleburnamine (**32**)

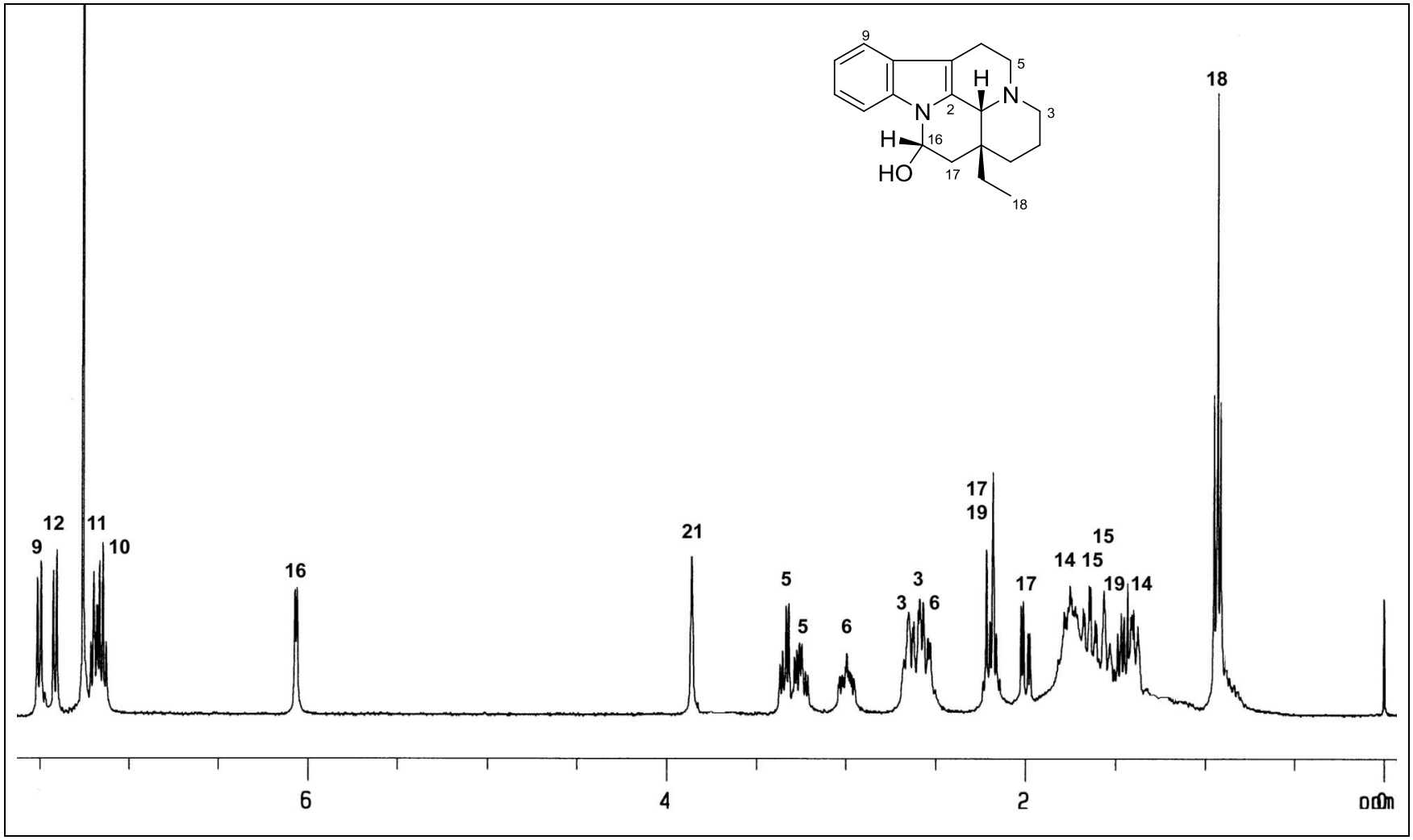


Figure 2.47: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (+)-isoeburnamine (**33**)

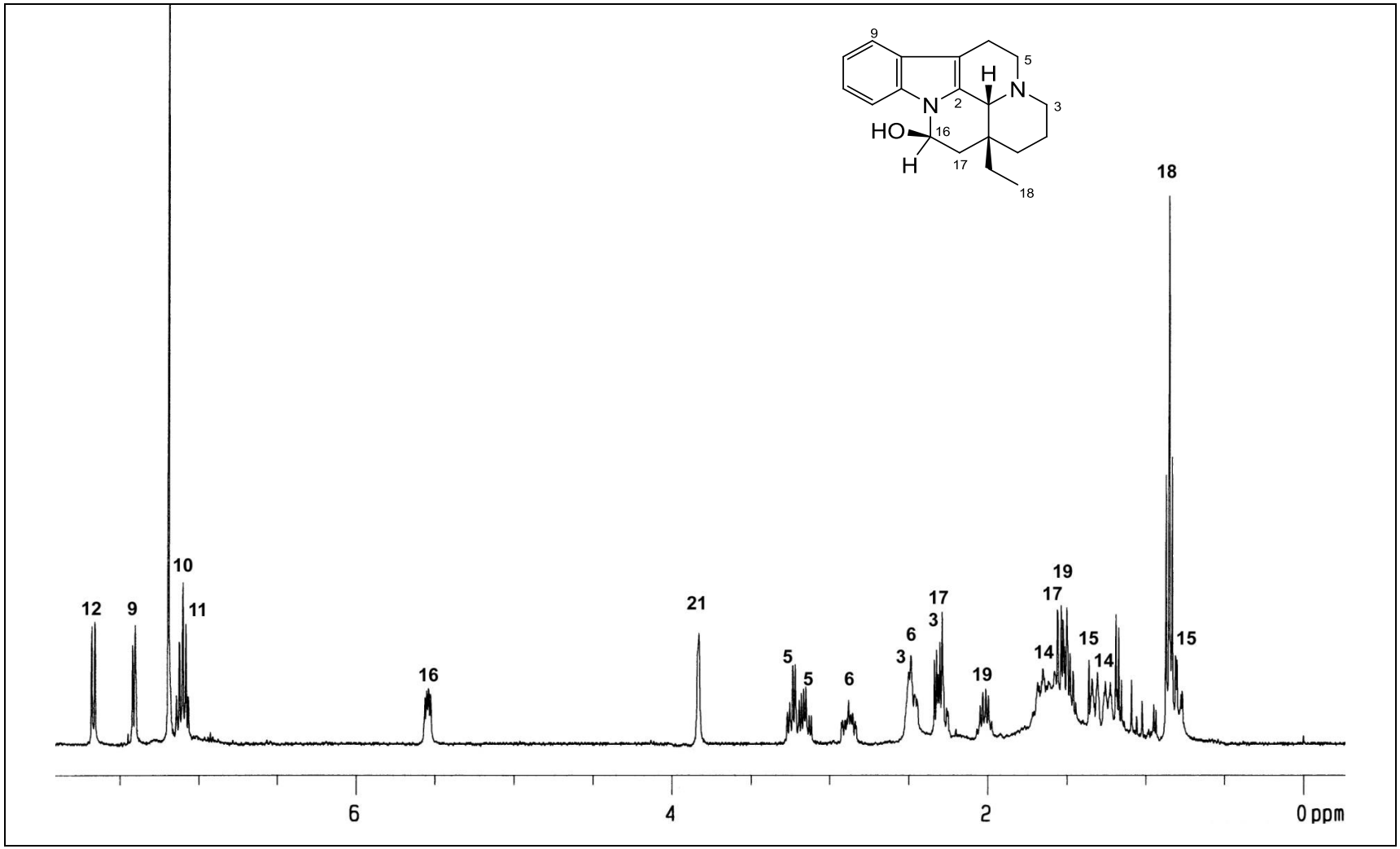


Figure 2.48: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (−)-eburnamine (**34**)

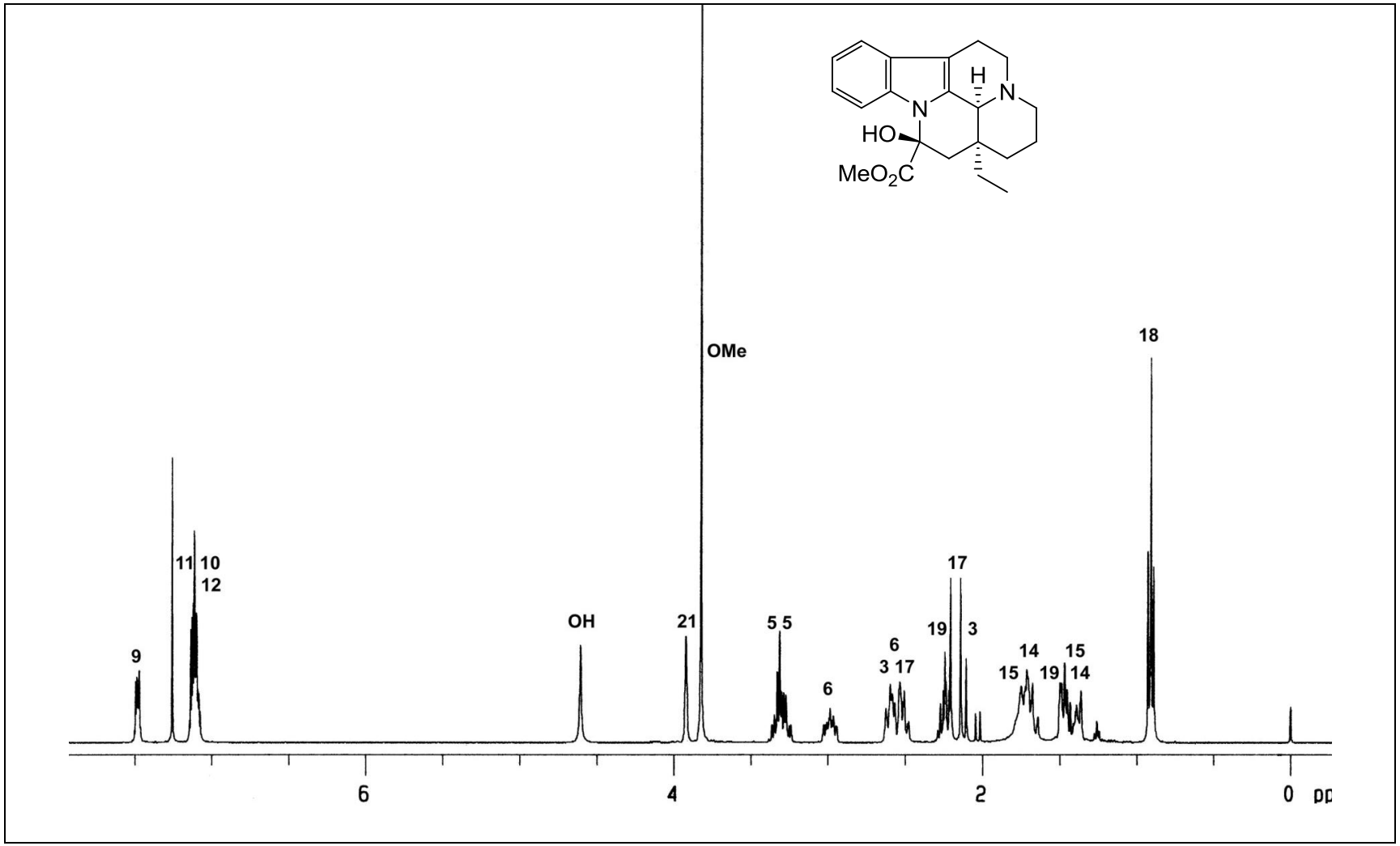


Figure 2.49: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (±)-vincamine (**35**)

2.1.5 Bisindole Alkaloids

2.1.5.1 Leucophyllidine (36)

Leucophyllidine (**36**)[137] was isolated in minute amounts as a light yellowish oil and subsequent crystallization from Et_2O–EtOAc, as pale yellowish crystals, mp 215–217 ^oC, $[\alpha]_D$ −138 ($CHCl_3$, *c* 0.18). The UV spectrum (230, 288, and 354 nm) indicated a composite chromophore from the superposition of indole and quinoline moieties,[322] while the IR spectrum showed the presence of only one functionality, *viz.*, an absorption due to OH at 3376 cm^{-1}. The EI mass spectrum of **36** showed an M^+ at *m/z* 572 (base peak), which analyzed for $C_{38}H_{44}N_4O$ (corresponding to a DBE value of 19), with other prominent fragment peaks due to loss of ethyl and C_4H_8N at *m/z* 543 and 502, respectively.

The ^1H NMR spectrum (Figure 2.53) showed signals due to six aromatic hydrogens, four of which correspond to the four contiguous hydrogens of an indole unit as indicated from the COSY spectrum. The remaining two aromatic hydrogens appeared as two singlets at δ 7.77 and 7.54. The ^1H NMR spectrum also revealed the presence of two ethyl and one vinyl side chain, two isolated methylenes and one isolated methine. The ^{13}C NMR data (Table 2.24) accounted for all 38 carbon resonances comprising 2 methyl, 14 methylene, 9 methine, and 13 quaternary carbons. Examination of the NMR chemical shifts, as well as the COSY and HETCOR data, revealed partial structures (unsubstituted indole, NCH_2CH_2, $NCH_2CH_2CH_2$, $NCHCH_2$, NCH, and CH_3CH_2) which indicated that one unit of the bisindole corresponds to an eburnane moiety. This attribution was readily confirmed by examination of the ^{13}C NMR spectrum as well as

the HMBC spectrum, where the signals corresponding to an eburnane half (eburnamine (**34**)) were clearly evident.[124,214] The signal due to H(16') was observed as a one-H multiplet at δ 5.77, suggesting branching of the bisindole from this carbon, a conclusion which was supported by the observed H(9) to C(16') three-bond correlation seen in the HMBC spectrum of **36** (Figure 2.50). Since the eburnane alkaloids present in this plant such as (–)-eburnamaline (**28**), (+)-eburnamonine (**29**), (+)-eburnamenine (**30**), *O*-methylisoeburnamine (**31**), *O*-methyleburnamine (**32**), (+)-isoeburnamine (**33**), and (–)-eburnamine (**34**), all belong to the 20β,21β-enantiomeric group, the eburnane half in leucophyllidine (**36**) is in all probability derived from (–)-eburnamine (**34**). The attachment of the other unit at C(16') is likely to be β, in analogy to the other *Aspidosperma-eburnea* bisindoles[188,223] with branching from the eburnane C(16').

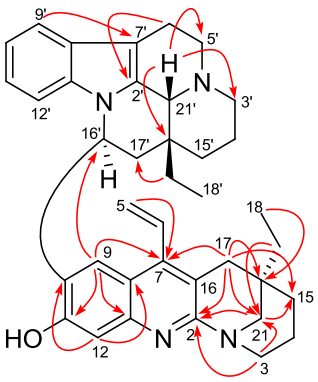


Figure 2.50: Selected HMBCs of **36**

The other unit constituting the bisindole, after discounting the eburnane half, incorporates an aromatic ring substituted at C(10) and C(11), from the observation of two aromatic singlets at δ 7.54 and 7.77. Other fragments associated with this monomeric unit includes an ethyl (δ 7.1, 35.0), and a vinyl (δ 123.1, 131.1) side chain. The OH group indicated in the IR spectrum constitutes one of the aromatic substituents, which is consistent with the observed shift of this carbon at δ 155.8, while the adjacent

aromatic carbon (δ 118.7) represents the site of eburnane substitution. The carbon shifts of the aromatic unit can be assigned based on the HMBC spectrum. The three-bond correlation from the aromatic signal at δ_H 7.54 to the eburnane C(16') (δ 49.7) and to another aromatic carbon at δ 143.9 (C(7)) allowed the assignment of this signal to H(9) and that at δ 7.77 to H(12). The correlation from H(9) to the signal at δ 155.8 establishes hydroxy-substitution to be at C(11) and hence eburnane substitution at C(10) (δ 118.7). The remaining correlations from H(9) and H(12) allowed the assignment of the other aromatic carbons (Figure 2.50). The low field resonance observed at δ 160.7 indicated the presence of an imine function and this, with the two remaining quaternary aromatic signals at δ 120.9 and 143.9, can be attributed to C(2), C(16), and C(7), respectively, of a quinoline chromophore. Attachment of the vinyl side chain is to C(7) due to the observed three-bond correlation from the vinylic H(5) to C(7). The NMR data also showed the presence of an isolated methylene and an isolated aminomethylene, in addition to an ethyl side chain attached to a quaternary carbon. The three-bond correlations observed from H(17) to C(21), H(21) to C(2), and the two bond correlation from H(17) to C(20) allowed the methylene, ethyl-substituted quaternary carbon, and the aminomethylene fragments to be linked to form a third ring fused to the vinylquinoline unit, constituting a tetrahydrobenzo[*b*][1,8]naphthyridine ring system.

This leaves a three-carbon fragment to complete assembly of the molecule. The COSY spectrum showed the presence of an NCH_2CH_2 fragment. This partial structure should in fact be part of the NC(3)–C(14)–C(15) fragment, but extensive overlap allowed only the NC(3)–C(14) fragment to be discerned. The presence of the C(15) methylenes as part of the NC(3)–C(14)–C(15) fragment linked from C(15) to C(20) can however be deduced indirectly from the correlations observed from H(21) and H(17) to C(15). The

observed correlation from H(3) to C(2) allowed the linking of this fragment from C(3) to N(4) to complete assembly of the fourth ring. The resulting tetracylic quinolinic structure unraveled corresponds to a new alkaloid skeleton. A search of the literature however, revealed that a vinyl-substituted quinoline alkaloid different to the quinolinic coupling partner in **36**, named strictigine (**467**), was isolated from *Rhazya stricta*.[323]

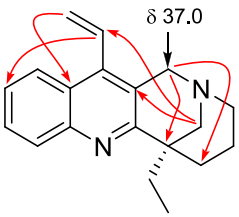


Figure 2.51: ^{4}J and ^{5}J HMBCs of **467**

Although the structure proposed for strictigine was different from that of the vinylquinoline moiety of leucophyllidine (**36**), the NMR data of the non-aromatic part of the molecule were virtually similar to those of the quinolinic coupling partner in **36**. A closer examination of the NMR data of strictigine revealed, in addition to a major incorrect assignment of the δ 37.0 carbon shift and the absence of the C(7) signal, an excessive number of ^{4}J and ^{5}J HMBCs (Figure 2.51), which in combination led to the wrong structural assignment.

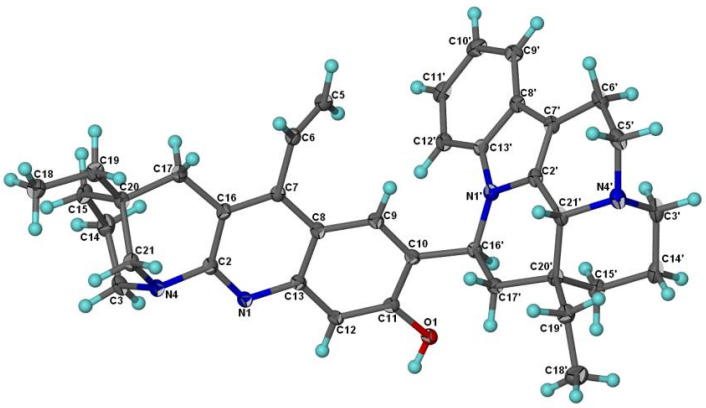
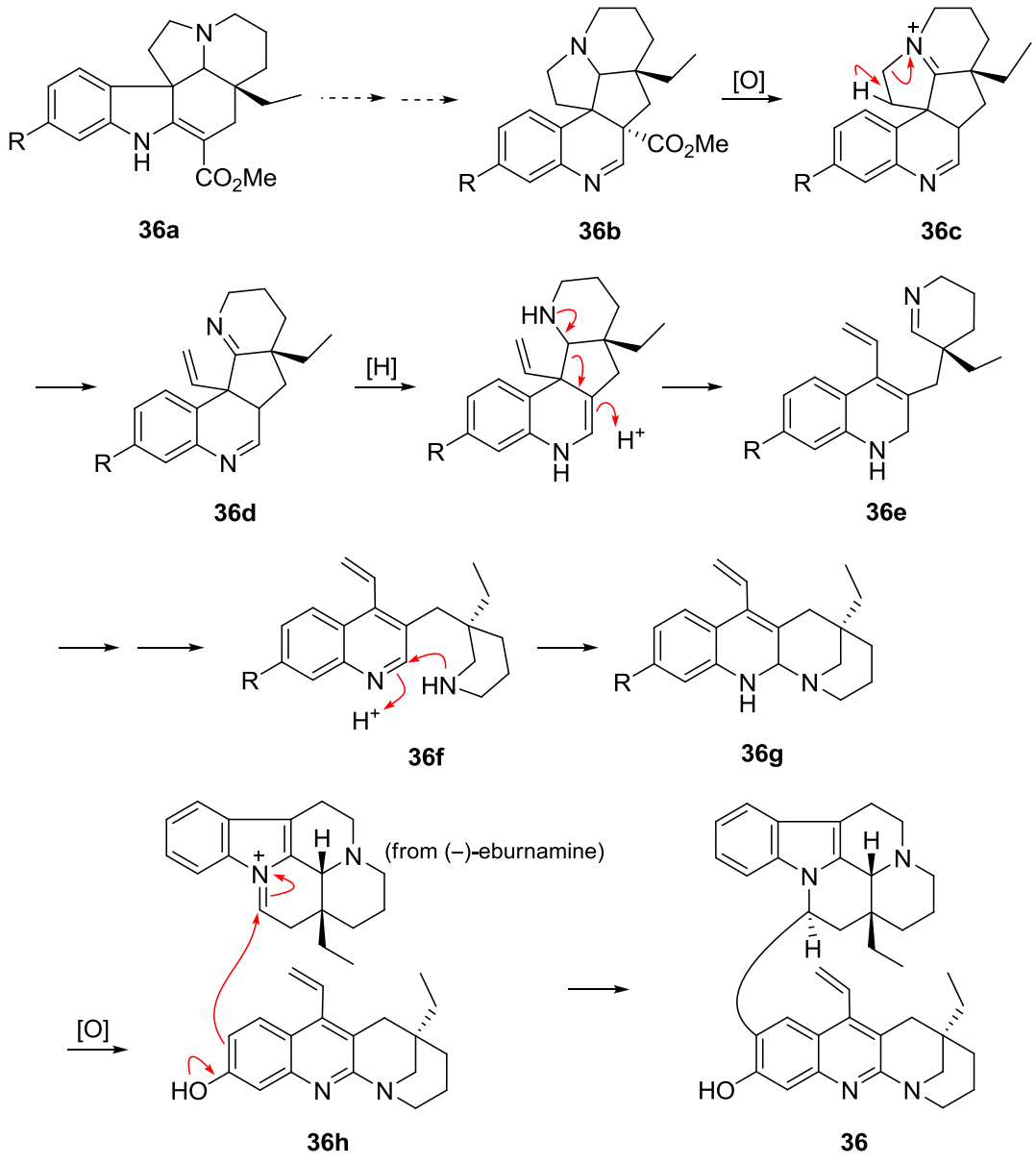


Figure 2.52: X-ray crystal structure of **36**

In order to secure unambiguous confirmation of the proposed structure of leucophyllidine (**36**), an X-ray diffraction analysis was carried out (Figure 2.52) which provided vindication of the structure proposed for **36** based on analysis of the spectroscopic data. The structure of leucophyllidine (**36**) is unprecedented on two counts. First, it represents the first member of a new structural subclass of the bisindole alkaloids based on the constituent monomeric halves. Secondly, the vinylquinoline half is distinguished by a novel skeleton incorporating an unprecedented tetrahydrobenzo[*b*][1,8]naphthyridine chromophore.



Scheme 2.5: A possible biogenetic pathway to **36**

A possible pathway to **36**[135] is presented in Scheme 2.5 from an *Aspidosperma* precursor (*e.g.*, 11-hydroxyvincadifformine **36a**).[324] Transformation of **36a** to the *Melodinus*-type alkaloid **36b** is well established.[325,326] Decarboxylation, followed by oxidation gives the iminium ion **36c**. Cleavage of the C(5)–N(4) bond (which has precedents in the thermally-induced transformations of kopsinic acid and secodine derivatives[327]) furnishes the ring-E *seco*-alkaloid **36d**. Reduction, followed in succession by a lone pair-assisted Grob-like fragmentation, leads to the vinyl-substituted dihydroquinoline derivative **36e**, which on aromatization following reduction of the imine, yields the vinylquinoline derivative **36f**. Ring closure *via* attack of the piperidine NH onto the imine carbon yields the tetracyclic dihydroquinoline **36g**, which on aromatization furnishes the vinylquinoline alkaloid incorporating a tetrahydrobenzo[*b*][1,8]naphthyridine core. Coupling of this novel vinylquinoline alkaloid **36h** with (–)-eburnamine (**34**) furnishes leucophyllidine (**36**).

Table 2.24: ^{1}H and ^{13}C NMR Data of Leucophyllidine (**36**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	160.7	2'	–	133.6
3	3.12 t (11)	55.6	3'	2.41 m	44.3
	3.80 m			2.62 m	
5	4.84 d (18)	123.1	5'	3.34 m	50.6
	5.32 d (12)			3.34 m	
6	6.50 dd (18, 12)	131.1	6'	2.62 m	17.1
				2.99 m	
7	–	143.9	7'	–	104.5
8	–	130.9	8'	–	128.3
9	7.54 s	123.5	9'	7.48 d (7.3)	117.7
10	–	118.7	10'	7.02 t (7.3)	118.9
11	–	155.8	11'	6.85 t (7.3)	120.2
12	7.77 s	110.1	12'	6.71 d (7.3)	112.4
13	–	147.2	13'	–	136.1
14	1.24 m	19.4	14'	1.36 m	20.4
	1.36 m			1.80 m	
15	1.45 m	36.0	15'	1.20 m	24.4
	1.69 m			1.36 m	
16	–	120.9	16'	5.77 m	49.7
17	2.39 m	36.4	17'	1.58 m	42.0
	2.58 m			2.56 m	
18	0.89 t (7)	7.1	18'	0.77 t (7)	7.5
19	1.27 m	35.0	19'	1.45 m	28.6
	1.27 m			2.06 m	
20	–	30.5	20'	–	34.7
21	2.88 d (12)	57.3	21'	4.05 s	59.3
	2.99 d (12)				

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HETCOR, HMBC, and NOESY/DNOE.

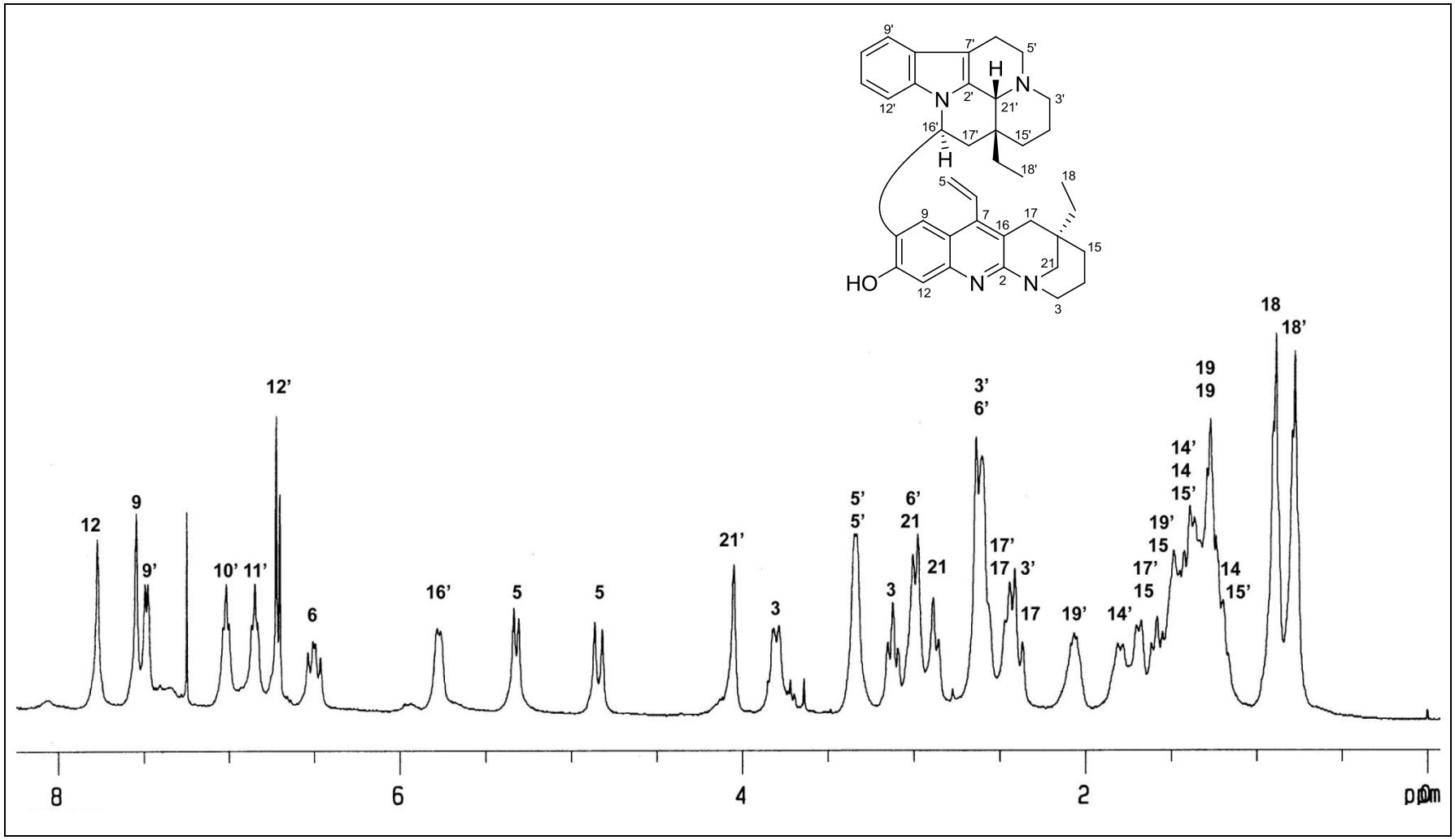
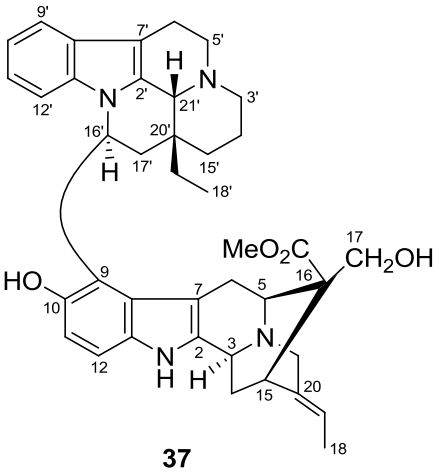


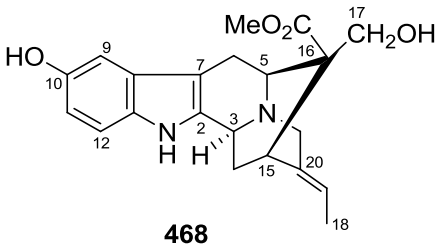
Figure 2.53: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leucophyllidine (**36**)

2.1.5.2 Leuconoline (37)

Leuconoline (**37**)[135] was isolated as a light yellowish oil and subsequently light yellowish crystals from EtOH, mp 223–224 ^{o}C, $[\alpha]_D$ +142 ($CHCl_3$, *c* 0.49). The IR spectrum indicated the presence of OH (3401 cm^{-1}) and ester carbonyl (1713 cm^{-1}) functions. The UV spectrum showed absorption maxima at 230 and 285 nm, characteristic of an indole chromophore. The EIMS showed a molecular ion at *m/z* 646, and HREIMS measurements established the molecular formula as $C_{40}H_{46}N_4O_4$. The ^{13}C NMR data (Table 2.25) of **37** gave a total of 40 carbon resonances (three methyl, eleven methylene, twelve methine, and fourteen quaternary carbons) in agreement with the molecular formula from HREIMS. The ^{1}H NMR data (Table 2.25) of **37** showed the presence of six aromatic hydrogens, four of which correspond to the four contiguous hydrogens of an indole unit as indicated from the COSY spectrum. The remaining two aromatic hydrogens were seen as a pair of AB doublets at δ 6.62 and 7.05.



37



468

The ^{1}H NMR spectrum (Figure 2.56) also showed the presence of a broad one-H singlet at δ 7.98 (exchanged with D_2O), a methoxy signal at δ 2.97 which is associated with a methyl ester moiety, signals due to an ethyl side chain at δ 0.97; 1.54, 2.27; another pair

of signals due to an ethylidene side chain at δ 1.64 and 5.38; an oxymethylene associated with a hydroxymethyl group at δ 3.59 and 3.80; a singlet at δ 4.05 due to an isolated methine, H(21'); and an isolated methylene signal at δ 3.52 and 3.61, due to H(21). The observation of ester carbonyl and oxymethylene resonances at δ 175.2 and δ 69.4, respectively, are consistent with the presence of the methyl ester and hydroxymethyl groups. The broad singlet at δ 7.98 is attributed to the indolic NH associated with the disubstituted indole moiety. This is based on the observed NOE between NH and H(12) (δ 7.05) of the disubstituted indole unit which also allowed assignment of the aromatic AB doublets to H(11) and H(12). Since the molecular formula showed the presence of four oxygen atoms and three have already been accounted for, the remaining oxygen must be due to a phenolic OH associated with the disubstituted indole moiety. This was further supported by acetylation (Ac_2O/DMAP), which yielded a diacetate derivative **37a** (δ_H 1.72 and 1.98; δ_C 20.2, 169.0; 20.9, 170.8; see Experimental Section).

Examination of the NMR chemical shifts as well as the 2-D COSY and HETCOR data revealed that one unit of the bisindole corresponds to an eburnane moiety. This is supported by examination of the ^{13}C NMR data which showed a close correspondence to those of eburnamine (**34**) or to bisindole alkaloids incorporating an eburnane half, such as leucophyllidine (**36**). The H(16') signal was observed as a doublet of doublets (*J* = 12, 4.4 Hz) indicating branching of the bisindole from C(16') of the eburnane unit. This conclusion receives additional support from the observation of long-range correlation from the eburnane H(16') to the aromatic C(10) of the other indole unit (*vide infra*). The configurations at C(20) and C(21) of the eburnane unit were deduced to be 20*R* and 21*R* (20β, 21β) on the basis of a presumed common biogenetic origin, since

the other eburnane alkaloids found in the plant are all belong to the 20*R*, 21*R* enantiomeric group.

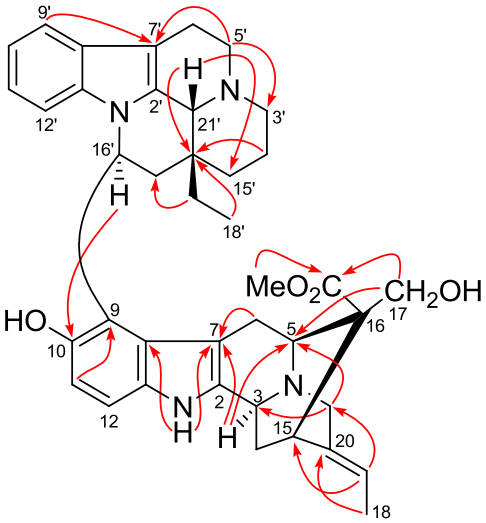


Figure 2.54: Selected HMBCs of **37**

The other unit constituting the bisindole, after discounting the eburnane half, incorporates a disubstituted indole moiety, an indolic NH, a methyl ester, a hydroxymethyl, an aminomethylene, an ethylidene side chain, as well as $NCHCH_2$ and $NCHCH_2CH$ partial structures. Examination of the NMR data as well as assembly of these fragments with the help of the HMBC data (Figure 2.54) revealed an alkaloid of the sarpagine subclass (*e.g.* 11-hydroxyakuammidine (**468**)). The unusual shielding of the ester methyl at δ 2.97 is in agreement with the configuration at C(16), which places the ester function in the shielding zone of the aromatic ring of the sarpagine unit. The location of hydroxy-substitution was deduced to be at C(10) from the observed three-bond H(16') (eburnane half) to C(10) (sarpagine half, δ 148.8) correlation observed in the HMBC spectrum. The bisindole is therefore branched from C(16') of the eburnane half to C(10) of the sarpagine half. The attachment of the sarpagine unit at the eburnane

C(16') is likely to be β in analogy to the other *Aspidosperma-eburnea* bisindoles with branching from the eburnane C(16'). This is also supported by the observed coupling constants for H(16') of 12 and 4.4 Hz which are consistent with an axial or α-oriented H(16') and diagnostic of eburnane alkaloids belonging to the eburnamine series, as opposed to those belonging to the diastereomeric (+)-isoeburnamine (**33**) (or *epi*-eburnamine) series. Leuconoline (**37**) represents the first example of a bisindole of the eburnane–sarpagine type.

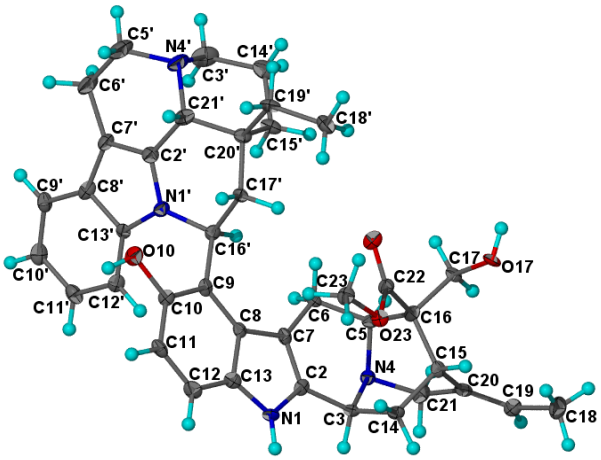


Figure 2.55: X-ray crystal structure of **37**

Since suitable crystals of leuconoline (**37**) were obtained, an X-ray diffraction was also carried out which provided further confirmation of the structure deduced from analysis of the spectroscopic data (Figure 2.55).

Table 2.25: ^{1}H and ^{13}C NMR Spectroscopic Data of Leuconoline (**37**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	138.8	2'	–	133.7
3	4.21 d (10)	50.5	3'	2.52 m	44.6
				2.64 m	
5	3.01 m	57.9	5'	3.29 m	50.9
				3.33 m	
6	3.01 m	27.6	6'	2.57 m	17.0
	3.31 m			3.02 m	
7	–	104.5	7'	–	107.0
8	–	124.7	8'	–	128.9
9	–	117.3	9'	7.43 d (7.6)	117.8
10	–	148.8	10'	7.01 td (7.6, 1)	120.0
11	6.62 d (8.5)	113.3	11'	6.74 td (7.6, 1)	121.2
12	7.05 d (8.5)	110.9	12'	6.57 d (8.3)	111.7
13	–	132.0	13'	–	137.7
14	1.87 m	29.9	14'	1.46 m	20.7
	2.63 m			1.79 m	
15	3.05 m	28.9	15'	1.21 td (13, 3)	24.0
16	–	50.8		1.56 m	
17	3.59 d (10.5)	69.4	16'	5.65 dd (12, 4.4)	51.4
	3.80 d (10.5)		17'	2.21 dd (14, 12)	39.5
18	1.64 d (7)	12.9		2.61 m	
19	5.38 q (7)	116.4	18'	0.97 t (7.6)	7.5
20	–	137.3	19'	1.54 m	29.1
21	3.52 d (17)	55.0		2.27 dq (14, 7)	
	3.61 d (17)		20'	–	35.3
NH	7.98 s	–	21'	4.05 s	59.7
CO_2*Me*	2.97 s	51.4			
CO_2Me	–	175.2			

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HETCOR, and HMBC.

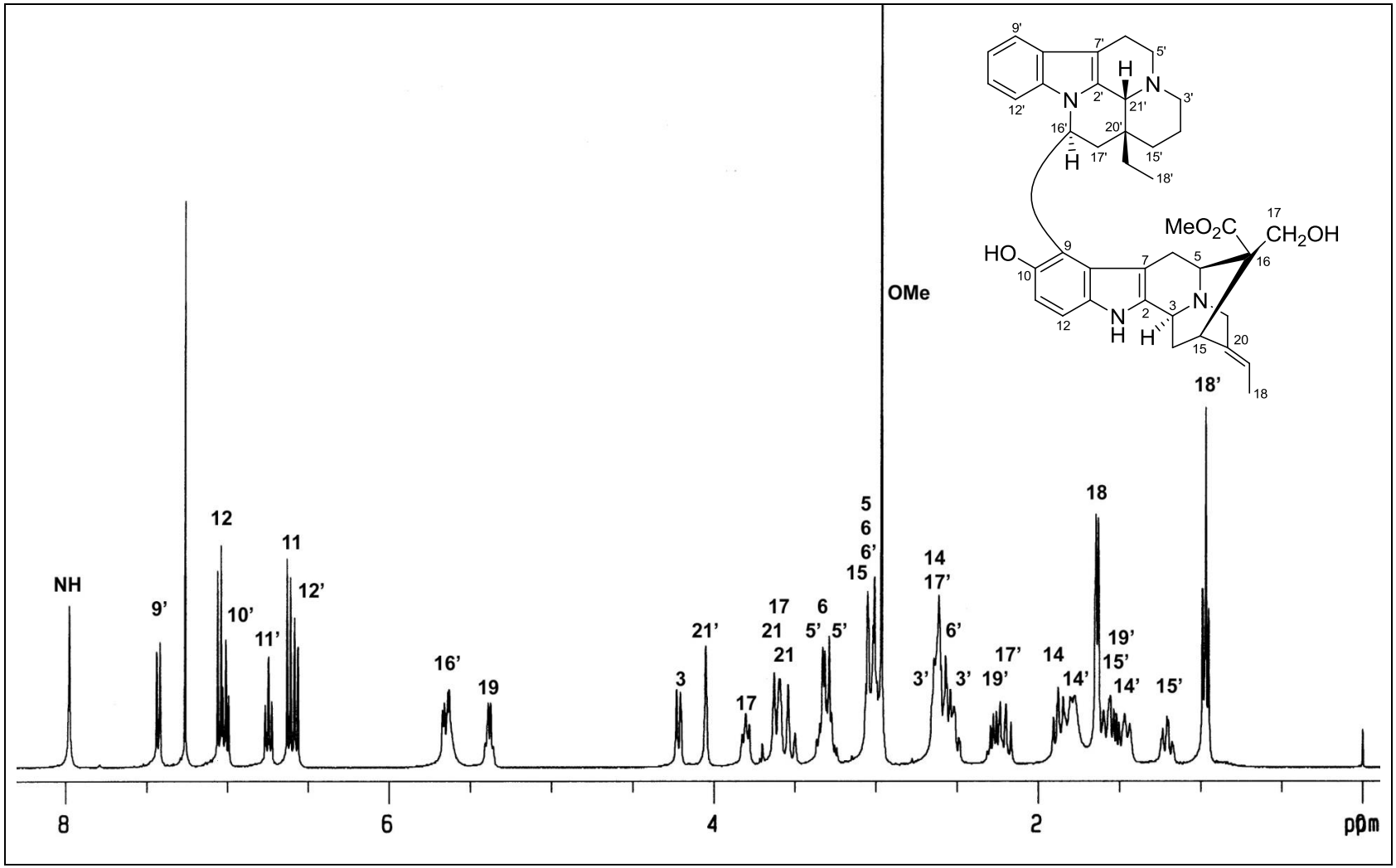
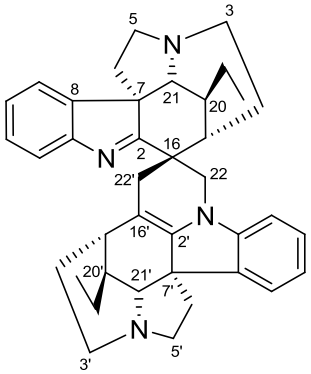


Figure 2.56: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leuconoline (**37**)

2.1.5.3 Leucofoline (38)

Leucofoline (**38**)[135] was isolated as a light yellowish oil, $[\alpha]_D$ +113 ($CHCl_3$, *c* 0.28). The UV spectrum showed absorption maxima at 214 and 273 nm indicating the presence of an indolenine chromophore. The ESIMS of **38** showed a quasi molecular ion at *m/z* 557, and HRESIMS measurements established the molecular formula as $C_{38}H_{44}N_4$ (DBE 19). The ^{13}C NMR data (Table 2.26) accounted for all of 38 carbon resonances, comprising two methyl, twelve methylene, fourteen methine, and ten quaternary carbons. The ^{1}H NMR spectrum (Figure 2.58) showed the presence of eight aromatic hydrogens corresponding to two unsubstituted aromatic moieties, and two isolated methylenes (δ_H 1.86, 3.30; δ_C 42.6; δ_H 3.75, 4.11; δ_C 48.4). In addition to the two aromatic CHCHCHCH units, the main partial structures revealed by the COSY and HSQC data were two $NCHCHCH_2CH_3$ fragments, which are characteristic of the N(4)–C(21)–C(20)–C(19)–C(18) fragment of the aspidospermatan- or condylocarpine-type alkaloids.



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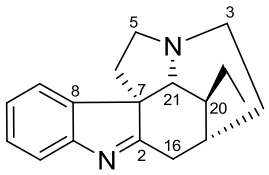
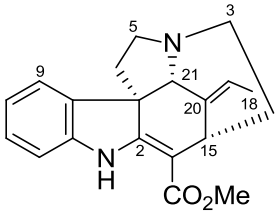
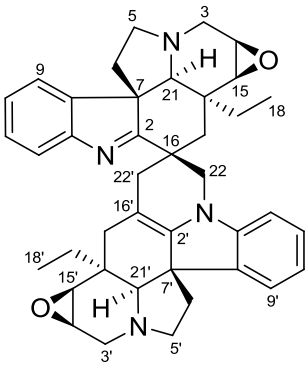


469



92



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Examination of the ^{1}H and ^{13}C NMR data showed that one unit of the bisindole corresponds to the known alkaloid, *epi*-condyfoline (**469**),[328] except for C(16) which is a quaternary carbon in **38** instead of a methylene in **469**. This provided the first indication that branching of the bisindole from this indolenine unit is from C(16), since there was no evidence of substitution at the other carbons of the condyfoline-like unit. Examination of the remaining fragments which correspond to those constituting the other condylocarpine unit, revealed a similar ring system as **469**, except for the presence of an enamine double bond instead of an indolenine. This left two isolated methylene groups, one each attached to the indolic N(1') and to C(16') of the second indole unit. This is consistent with the observed shifts of these methylenes (δ 3.75, 4.11, NCH_2; δ 1.86, 3.30, CCH_2) as well as the HMBC data (Figure 2.57). Both of these methylenes are linked to C(16) of the first or condyfoline-like unit to forge a tetrahydropyridine ring incorporating C(16) as a spirocyclic center. This was supported by the observed ^{2}J and ^{3}J correlations from H(22') to C(16), and from H(22') to C(2), respectively, as seen in the HMBC spectrum. This mode of branching in leucofoline (**38**) is somewhat similar to that in the *Aspidosperma–Aspidosperma* bisindole, anhydrohazuntiphyllidine (**470**),[329] and is also in agreement with the HMBC data.

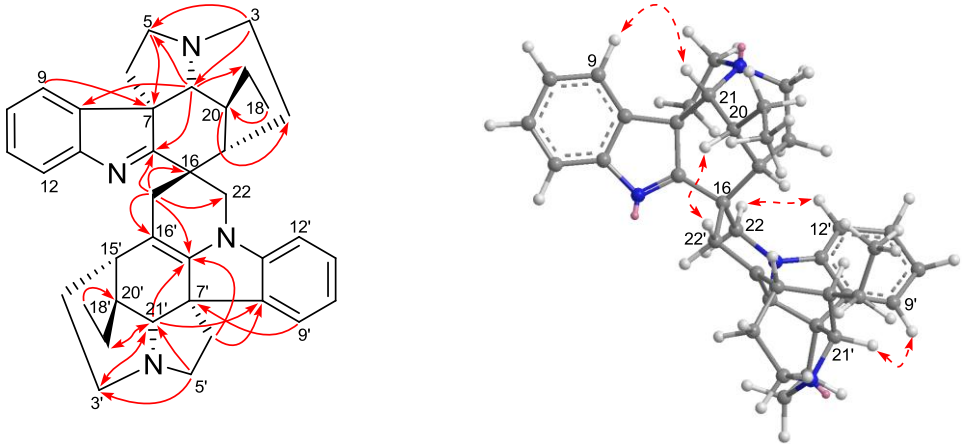
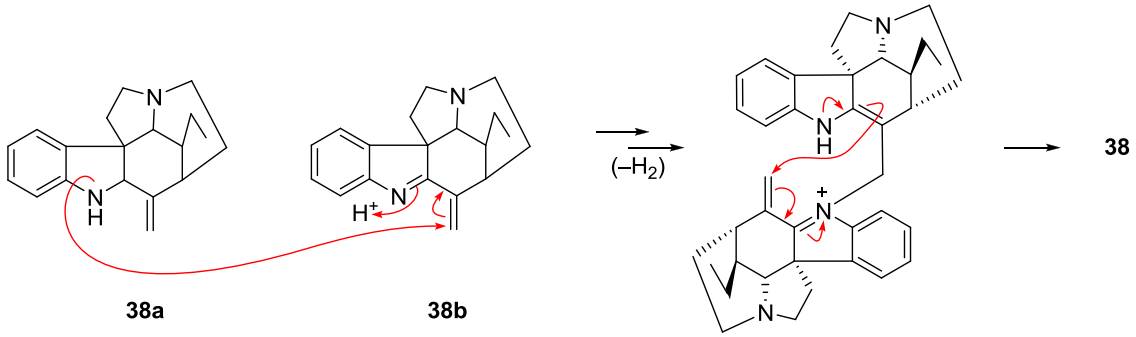


Figure 2.57: Selected HMBCs and NOEs of **38** (= HMBC; = NOE)

The NOE data showed that the relative configurations of the monomeric units are similar to those of condylocarpine (**92**). The configuration at the spirocyclic center, C(16), was determined to be *R*, from the observed H(20)/H(22a) reciprocal NOEs, which are possible only if C(16) is *R* (Figure 2.57). In the converse case (C(16*S*)), these two hydrogens will be directed away from each other and would therefore not be expected to show any NOE (Figure 2.57).



Scheme 2.6: A possible biogenetic pathway to **38**

Leucofoline (**38**) represents the first example of a bisindole of the aspidospermatan–aspidospermatan type. A possible pathway to **38** is shown in Scheme 2.6 involving conjugate addition *via* the indolic nitrogen of the condylocarpine-type precursor **38a** (or 16-methylenecondyfoline) onto the imine **38b**, to effect the N(1′) to C(16) link, followed by a subsequent conjugate addition of an enamine to forge the spirocyclic ring system.

Table 2.26: ^{1}H and ^{13}C NMR Spectroscopic Data of Leucofoline (**38**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	191.3	2'	–	147.9
3	3.26 m	58.7	3'	2.78 m	45.2
	3.26 m			2.92 m	
5	2.86 m	46.3	5'	2.73 m	54.2
	3.21 m			2.89 m	
6	1.95 td (13, 5)	36.4	6'	1.57 m	41.2
	2.96 m			2.71 m	
7	–	66.7	7'	–	52.7
8	–	146.9	8'	–	136.7
9	7.29 d (7)	120.3	9'	7.08 d (7)	120.0
10	7.17 t (7)	125.9	10'	6.77 t (7)	119.5
11	7.28 t (7)	127.7	11'	7.09 t (7)	126.9
12	7.46 d (7)	120.2	12'	6.63 d (7)	107.7
13	–	153.4	13'	–	149.2
14	1.72 m	21.6	14'	1.52 m	19.9
	1.72 m			1.90 m	
15	2.02 m	36.0	15'	2.02 m	36.0
16	–	44.3	16'	–	110.5
18	0.74 t (7)	12.0	18'	0.90 t (7)	12.3
19	1.54 m	24.9	19'	1.76 m	24.4
	1.54 m			1.76 m	
20	1.07 m	38.4	20'	1.31 m	41.8
21	3.64 s	71.3	21'	3.56 s	65.0
22a	3.75 m	48.4	22'a	1.86 d (15)	42.6
22b	4.11 d (12)		22'b	3.30 m	

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HSQC, and HMBC.

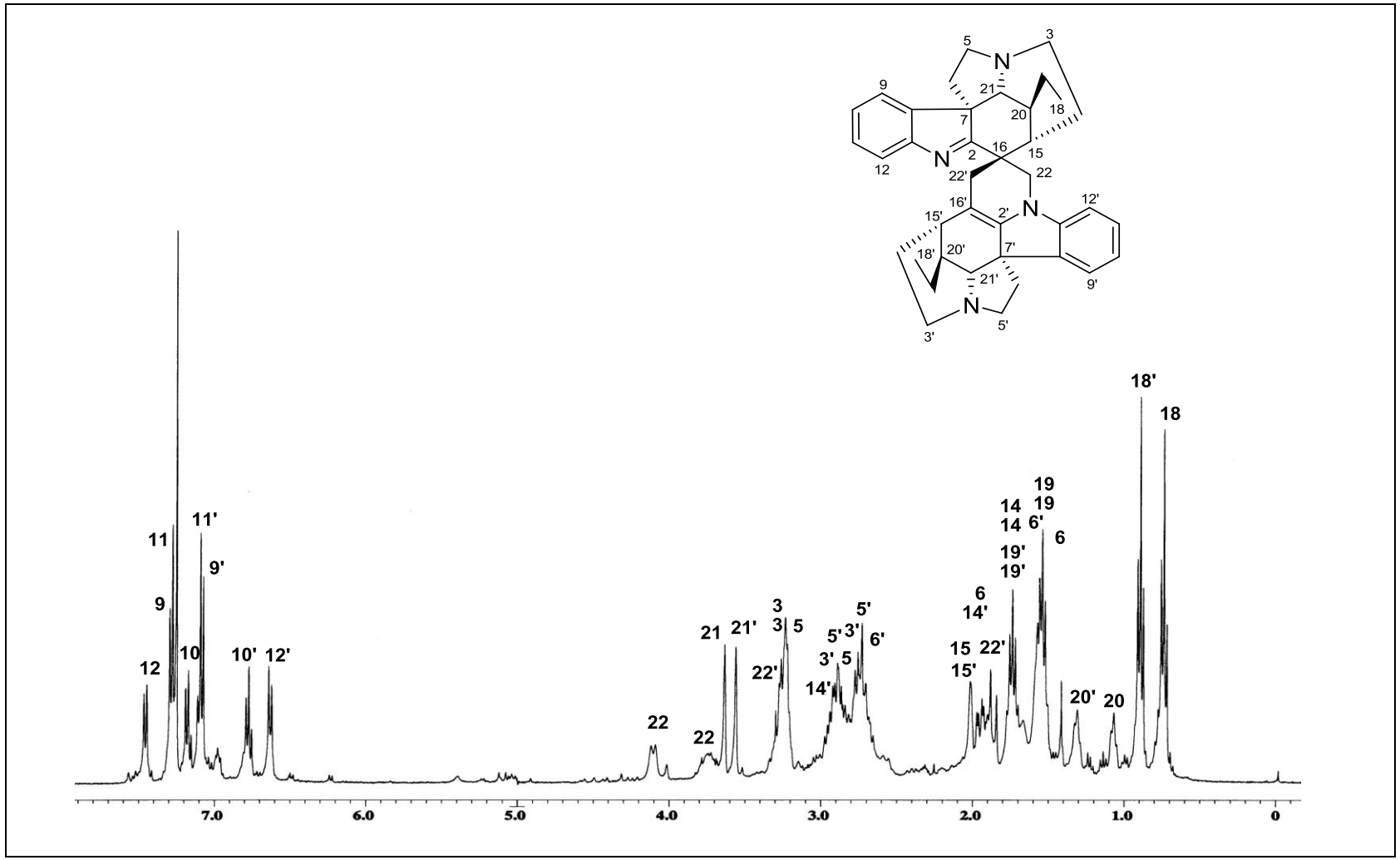
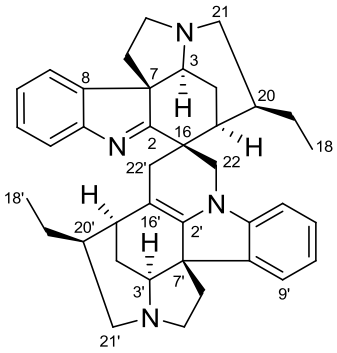


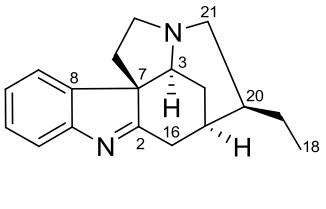
Figure 2.58: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leucofoline (**38**)

2.1.5.4 Leucoridine A (39)

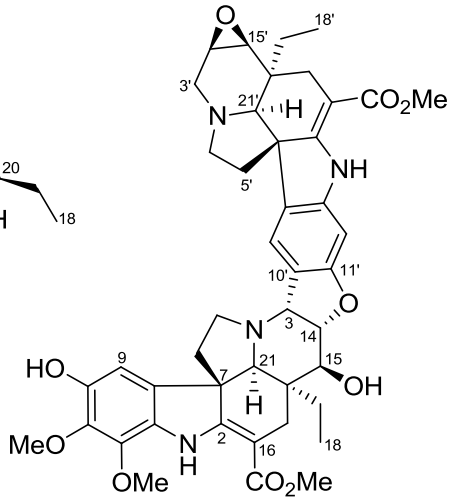
Leucoridine A (**39**)[138] was obtained as a light yellowish oil, with $[\alpha]_D$ −29 ($CHCl_3$, *c* 0.26). The UV spectrum showed absorption maxima at 213 and 267 nm, characteristic of an indolenine chromophore. The ESIMS of **39** showed an $[M + H]^+$ peak at *m*/*z* 557, and HRESIMS measurements yielded the molecular formula $C_{38}H_{44}N_4$ (19 DBE).



39



471



472

The ^{13}C NMR data (Table 2.28) accounted for 38 carbon resonances, comprising two methyl, 12 methylene, 14 methine, and 10 quaternary carbons. The presence of the imine function was supported by the observed carbon resonance at δ 188.0, while the presence of a tetrasubstituted double bond associated with an enamine function was seen at δ 110.2 and 147.8. The ^1H NMR data (Table 2.27) showed the presence of eight aromatic hydrogens corresponding to two disubstituted aromatic moieties (δ 7.30, dd, *J* = 7.3, 1 Hz, H(9); 7.17, td, *J* = 7.3, 1 Hz, H(10); 7.26, td, *J* = 7.3, 1 Hz, H(11); 7.36, dd, *J* = 7.3, 1 Hz, H(12); 7.08, dd, *J* = 7.3, 1 Hz, H(9′); 6.83, td, *J* = 7.3, 1 Hz, H(10′); 7.11, td, *J* = 7.3, 1 Hz, H(11′); 6.68, dd, *J* = 7.3, 1 Hz, H(12′)), two ethyl side chains (δ 1.00, t, *J* = 7.3 Hz, H(18); 1.57, m, H(19); 0.99, t, *J* = 7.3 Hz, H(18′); 1.75, m, H(19′)), and

two isolated methylenes (δ 3.01, d, *J* = 10 Hz, H(22); 4.59, d, *J* = 10 Hz, H(22); 2.03, m, H(22′); 2.91, d, *J* = 13 Hz, H(22′)).

The COSY and HSQC data disclosed the presence of the following partial structures: two NCH_2CH_2, two $NCHCH_2CH$, and one $NCH_2CHCH_2CH_3$. Another $NCH_2CHCH_2CH_3$ fragment could not be discerned from the COSY spectrum alone but was deduced with the aid of HMBC data (three-bond correlations from H(18) to C(20) and from H(19) to C(21)). The ^{1}H and ^{13}C NMR shifts indicated that the two sets of partial structures correspond to the presence of two strychnan units constituting the bisindole. The chemical shifts of one of these units (the indolenine-containing half) showed a close correspondence to those of the known *Strychnos* alkaloid tubifoline (**471**),[309] except for the distinct change involving C(16), which is a quaternary center in **39** instead of a methylene in tubifoline (**471**). This provided an early indication that branching of the bisindole from this indolenine unit is from C(16), since there was no evidence of substitution at the other carbons of the tubifoline-like unit. Examination of the remaining fragments that correspond to those constituting the other strychnan unit revealed a similar ring system to tubifoline (**471**), except for the presence of an enamine double bond instead of an indolenine.

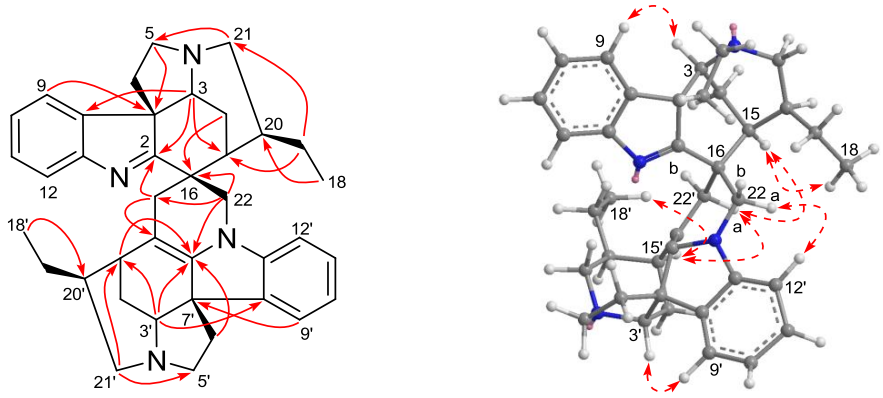


Figure 2.59: Selected HMBCs and NOEs of **39** (= HMBC; = NOE)

This left two isolated methylene groups, one each attached to the indolic nitrogen N(1′) and to C(16′) of the second strychnan unit. This is consistent with the observed shifts of these methylenes (δ 3.01, 4.59, NCH_2; δ 2.03, 2.91, CCH_2) as well as the HMBC data (Figure 2.59). Both of these methylenes are linked to C(16) of the first or tubifoline-like unit to forge a tetrahydropyridine ring incorporating C(16) as a spirocyclic center. This was supported by the observed ^2J and ^3J correlations from H(22) to C(16) and from H(22′) to C(2), respectively, as seen in the HMBC spectrum. The proposed structure is entirely consistent with the full HMBC data (Figure 2.59). The relative configurations at the various stereogenic centers in the strychnan moieties were established from NOEs (Figure 2.59) and analysis of the vicinal coupling constants, in the same manner as that carried out previously for leuconicine A (**2**).[134] This leaves the configuration at the spirocyclic C(16) to be determined.

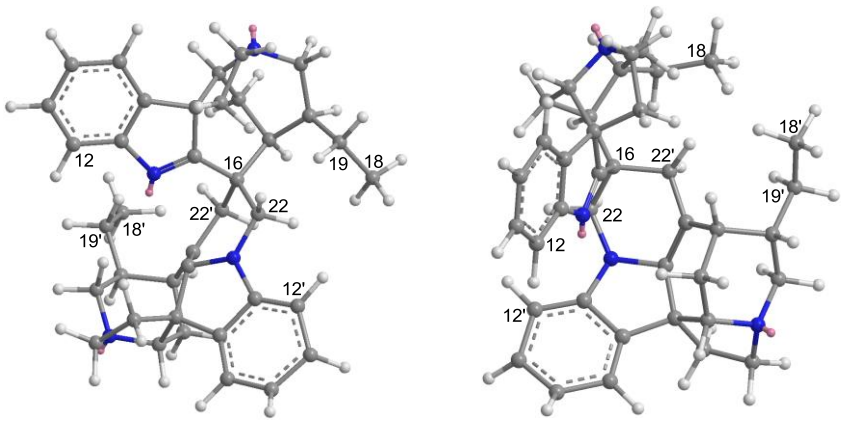
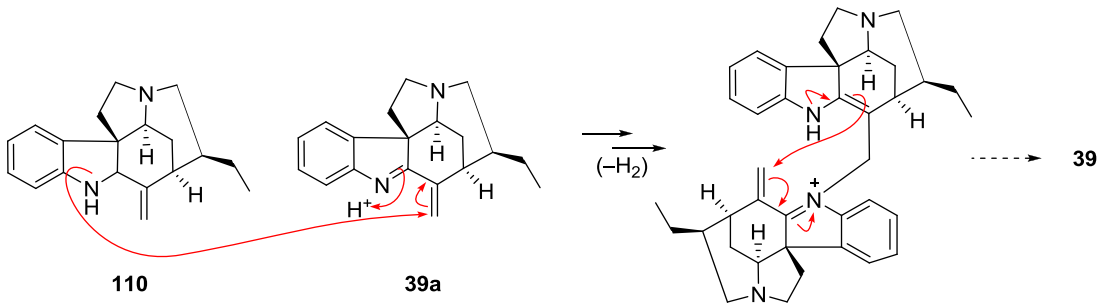


Figure 2.60: The 16*S* and 16*R* stereoisomers of **39**

The two alternative 16*S* and 16*R* stereoisomers are shown in Figure 2.60. The H(6)/H(22) NOE, previously used to establish the relative configuration (16*S*) in the related *Aspidosperma-Aspidosperma* bisindole anhydrohazuntiphyllidine (**470**),[329] could not be applied in the present instance due to the overlap of the H(6) and H(22) signals, although the presence of the alternative H(15)/H(22′a) and H(15′)/H(22′a), respectively

NOESY cross-peaks was suggestive of the 16*S* epimer. Additional support for the 16*S* configuration was deduced from the following evidence. In the case of the 16*S* epimer, examination of models revealed that the two indole units are situated in approximately the same plane, with the aromatic rings located at opposite ends and pointing in opposite directions (H(12) and H(12′) pointing in opposite directions), whereas in the 16*R* epimer, folding of the second indole unit results in H(12) of the tubifoline-like unit pointing into the aromatic ring of the second unit (Figure 2.60). This would result in clear anisotropy experienced by H(12), which would cause the H(12) resonance to be shifted significantly upfield compared with H(12′) in the ^{1}H NMR spectrum (Figure 2.62), an effect previously observed in the bisindole conophylline (**472**)[330] (H(9) in conophylline (**472**) seen at δ 5.55). In the present case, the chemical shifts of H(12) and H(12′) were seen at δ 7.36 and 6.68, respectively, (the H(12) resonance was in fact slightly downfield compared to H(12′)), with no evidence of any upfield shift as a result of anisotropy caused by the other aromatic ring. On the basis of the above lines of evidence, the relative configuration of the spirocyclic C(16) was assigned as *S*.



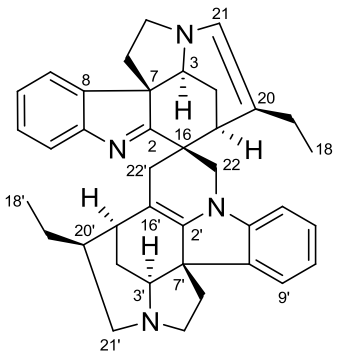
Scheme 2.7: A possible biogenetic pathway to **39**

A possible origin of the basic ring system of **39**, which are characterized by branching of one unit from a common spirocyclic carbon, C(16), is shown in Scheme 2.7, involving conjugate addition *via* the indolic nitrogen of anhydropereirine (**110**) (*vide infra*) onto the dihydrovalparicine derivative **39a**, to effect the N(1′) to C(16) link,

followed by a subsequent conjugate addition of an enamine to forge the spirocyclic ring system.

2.1.5.5 Leucoridine B (40)

Leucoridine B (**40**)[138] was isolated as a light yellowish oil, $[\alpha]_D$ +56 ($CHCl_3$, *c* 0.29). The UV spectrum showed absorption maxima at 215, 268, and 329 nm, consistent with the presence of indolenine and methyleneindoline chromophores, while the IR spectrum was similar to that of **39**. The ESIMS of **40** showed a quasi molecular ion at *m*/*z* 555, and HRESIMS measurements established the molecular formula as $C_{38}H_{42}N_4$ (DBE 20), *i.e.*, two mass units less than that of **39**. The ^1H and ^{13}C NMR data of **40** (Tables 2.27 and 2.28, respectively) were generally similar to those of **39**. However, the ^{13}C NMR spectrum of **40** indicated the presence of an additional double bond from the resonances at δ 124.1 and 131.9, corresponding to olefinic quaternary and methine carbons, respectively.



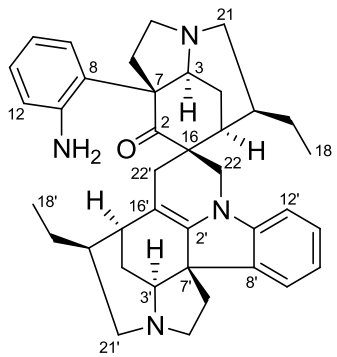
40

Comparison of the ^{13}C NMR spectrum with that of **39** showed that while the chemical shifts of the other carbons were essentially unchanged, those of C(20) and C(21) (of the tubifoline-like half) have undergone substantial shifts to the lower field sp^2 region,

indicating that these carbons correspond to the site of unsaturation. This was also supported by the observed three-bond correlations from H(3) and H(15) to C(21) in the HMBC spectrum. The signal due to H(20), seen in the ^{1}H NMR spectrum of **39** (δ 2.00), was absent in that of **40**. Instead, a new olefinic H signal corresponding to H(21), was observed as a singlet at δ 5.85 in the ^{1}H NMR spectrum (Figure 2.63) of **40**, in place of the two C(21) methylene signals previously seen for **39** at δ 2.78 and 3.41. Corresponding changes also occurred in the signals due to H(19), which in **40** were seen at δ 1.95 as a multiplet and at δ 2.08 as a doublet of quartets (J = 14, 7.3 Hz). These features are all consistent with the presence of a double bond across C(20) and C(21).

2.1.5.6 Leucoridine C (41)

Leucoridine C (**41**)[138] was isolated as a light yellowish oil, $[\alpha]_D$ −61 ($CHCl_3$, *c* 0.26). The UV spectrum was different from those of **39** and **40**, showing absorption maxima at 206, 250, and 275 nm, while the IR spectrum indicated the presence of primary amine (3414, 3358 cm^{-1}) and ketone (1686 cm^{-1}) functionalities. The ESIMS of **41** showed a quasi molecular ion at *m*/*z* 575, and HRESIMS measurements established the molecular formula as $C_{38}H_{46}N_4O$ (DBE 18).



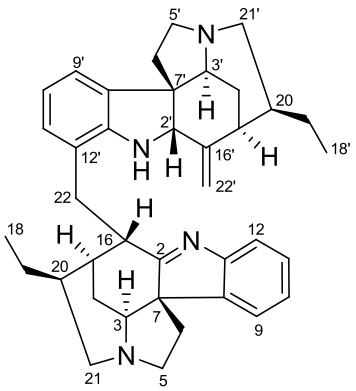
41

Comparison of the ^{13}C NMR data of **41** (Table 2.28) with those of **39** showed that the imine function in **39** (δ 188.0, C(2)) has been replaced by a ketone function (δ 215.7, C(2)). Similarly, comparison of the ^{1}H NMR spectrum of **41** with that of **39** indicated that the major difference was the appearance of two exchangeable hydrogens as a broad peak at δ 4.85, which was attributed to the presence of a primary amine (NH_2) group, which was also detected in the IR spectrum. Other changes in the ^{13}C NMR spectrum involved the shifts of C(7) (δ 60.6), and C(16) (δ 52.4), which are α to C(2), and C(13) (δ 147.5), to which the amino group is attached in compound **41**. These changes are consistent with hydrolytic cleavage of the N(1)–C(2) imine linkage of **39** to yield a primary amine and a ketone function. The ready detection of the NH_2 signal in the ^{1}H NMR spectrum is probably due to intramolecular H-bonding of the amine hydrogens with the proximate ketone function at C(2). Another significant change involved the ethyl hydrogens of the other strychnan moiety. These hydrogens have been significantly shifted upfield, in particular the methylene hydrogens, H(19′) (δ –0.11, –0.13). This is likely the result of anisotropy due to the carbonyl function at C(2), as a consequence of the new conformation adopted in the seco compound **41**.

The configurations at the spirocyclic C(16) in compounds **40** and **41** were deduced to be similar, *i.e.*, 16*S*, to that in compound **39** for the same reasons that were discussed in the case of **39** (*vide supra*). In the case of compound **41**, however, the observed anisotropic shielding of the ethyl hydrogens provide further support for the 16*S* configuration of the spirocyclic C(16), since if the C(16) configuration is *R*, the ethyl side chain of the second strychnan moiety would be directed away, and therefore too far removed from the tubifoline unit (Figure 2.60) to experience anisotropic effects.

2.1.5.7 Leucoridine D (42)

Leucoridine D (**42**)[138] was isolated as a light yellowish oil, $[\alpha]_D$ +6 ($CHCl_3$, *c* 0.40). The UV spectrum showed absorption maxima at 213, 253, and 299 nm, indicating the presence of indolenine and dihydroindole chromophores, while the IR spectrum indicated the presence of an indolic NH (3246 cm^{-1}). The ESIMS of **42** showed a quasi molecular ion at *m*/*z* 559, and HRESIMS measurements established the molecular formula as $C_{38}H_{46}N_4$ (DBE 18). The ^{13}C NMR data (Table 2.28) accounted for 38 carbon resonances, comprising two methyl, 12 methylene, 15 methine, and nine quaternary carbons.



42

The presence of the imine function was supported by the observed carbon resonance at δ 192.7, while the presence of a gem-disubstituted double bond was indicated by the signals seen at δ 115.7 and 146.9. Aside from these, the 12 remaining low-field sp^2 carbon resonances can be attributed to the presence of two aromatic rings associated with two indole moieties. The ^1H NMR data (Table 2.27) showed the presence of seven aromatic hydrogens (δ 7.30, dd, *J* = 7.6, 1 Hz, H(9); 7.19, td, *J* = 7.6, 1 Hz, H(10); 7.32, td, *J* = 7.6, 1 Hz, H(11); 7.54, dd, *J* = 7.6, 1 Hz, H(12); 6.90, d, *J* = 7.6 Hz, H(9′); 6.70, t, *J* = 7.6 Hz, H(10′); 6.92, d, *J* = 7.6 Hz, H(11′)), one indolic NH as a doublet at δ 6.85 (*J* = 5 Hz), two ethyl side chains (δ 1.03, t, *J* = 7.3 Hz, H(18); 1.43, m, H(19); 1.56, m,

H(19); 1.00, t, *J* = 7.3 Hz, H(18′); 1.26, m, H(19′); 1.43, m, H(19′)), and two singlets at δ 5.06 and 5.40 due to the geminal hydrogens of an exocyclic double bond. Since only seven aromatic hydrogens are present, branching of the bisindole must be from one of the aromatic carbons. The NMR shifts showed that one unit of the bisindole corresponds to the same tubifoline-like unit as in the previous three alkaloids (**39**–**41**), except that in compound **42**, C(16) was a methine and not a quaternary center as in the previous three alkaloids (**39**–**41**).

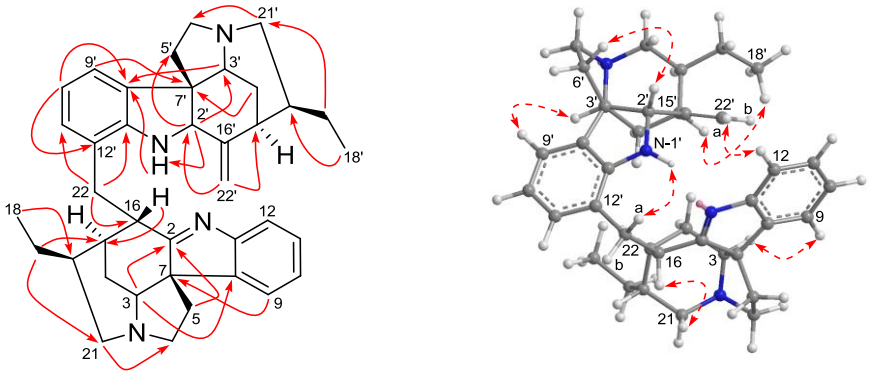
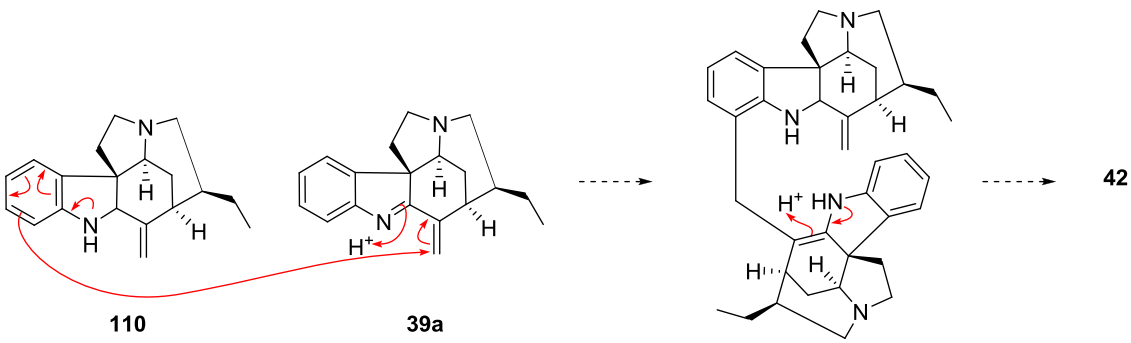


Figure 2.61: Selected HMBCs and NOEs of **42** (= HMBC; = NOE)

In addition, examination of the NMR data of the other monomeric unit yielded a structure that corresponded to the strychnan compound anhydropereirine (or anhydrogeissoschizoline) (**110**),[331] previously obtained as a dehydration product of pereirine (or geissoschizoline).[331,332] All four aromatic shifts of the tubifoline-like unit were seen, while only three contiguous aromatic hydrogens of the anhydropereirine-like unit were present. These were assigned to the C(9′)–C(10′)–C(11′) fragment from the observed NOE between H(9′) and H(3′) of the anhydropereirine unit. Branching of the bisindole is therefore from C(16) of the tubifoline-like unit to C(12′) of the anhydrogeissoschizoline unit. The 2-D NMR data (COSY, HSQC, and HMBC) revealed all the partial structures associated with the two strychnan halves constituting

the bisindole, except for the presence of an additional methylene (δ_C 35.0, δ_H 2.50, 3.40), which is attributed to the methylene bridge linking the two halves from C(12′) of the anhydropereirine unit to C(16) of the tubifoline-like unit. This assignment is consistent with the observed ^3J and ^2J correlations from H(22) to C(11′) and C(13′) and from H(22) to C(16), respectively, in the HMBC spectrum (Figure 2.61). The relative configuration of the stereogenic centers in the two strychnan halves were shown by NOE to correspond to those in the constituent monomers, tubifoline (**471**) and anhydropereirine/geissoschizoline (**110**) (Figure 2.61). The relative configuration at the branching point, C(16), was demonstrated by NOE (Figure 2.61) as follows. First, the observed reciprocal NOEs between H(16) and H(21β) are only possible if H(16) is β (16*S*), since, if H(16) is *R*, the two hydrogens will be located on opposite faces of the molecule and too far removed for NOEs to be observed. Similarly, the observed reciprocal NOEs between H(22a) and N(1′)-H, and between H(12) and H(22′a), are only possible if H(16) is β.



Scheme 2.8: A possible biogenetic pathway to **42**

A possible biogenetic origin of **42** is shown in Scheme 2.8, involving the same coupling partners as in the proposed biogenetic route to the bisindoles **39**–**41** (*vide supra*). In the case of **42**, the sequence is initiated by conjugate addition of the nucleophilic *ortho* carbon of the anhydropereirine unit (**110**) onto the dihydrovalparicine moiety **39a**.

Table 2.27: ^{1}H NMR Spectroscopic Data of Leucoridines A–D (**39**–**42**)[a]

H	**39**	**40**	**41**	**42**
3	3.74 br s	3.79 br s	3.75 br s	3.69 br s
5β	2.98 m	3.43 td (12, 5)	2.84 td (13, 3)	3.15 m
5α	3.32 m	3.54 dd (12, 6.5)	2.84 td (13, 3)	3.15 m
6α	2.13 dd (13, 4)	1.57 m	2.13 m	1.86 m
6β	3.05 m	2.65 td (13, 5.6)	3.44 dt (14, 9)	2.64 td (12, 7)
9	7.30 dd (7.3, 1)	7.30 d (7.6)	7.19 d (8)	7.30 dd (7.6, 1)
10	7.17 td (7.3, 1)	7.19 t (7.6)	6.65 t (7.7)	7.19 td (7.6, 1)
11	7.26 td (7.3, 1)	7.31 t (7.6)	6.96 t (7.7)	7.32 td (7.6, 1)
12	7.36 dd (7.3, 1)	7.39 d (7.6)	6.56 d (7)	7.54 dd (7.6, 1)
14*R*	1.32 br d (14)	1.60 m	2.33 dt (14, 3)	1.56 m
14*S*	1.70 br d (14)	1.95 m	2.98 m	1.56 m
15	2.00 m	2.16 m	2.00 m	2.04 m
16	–	–	–	2.97 m
18	1.00 t (7.3)	1.03 t (7.3)	1.00 t (7)	1.03 t (7.3)
19	1.57 m	1.95 m	1.48 m	1.43 m
	1.57 m	2.08 dq (14, 7.3)	1.64 m	1.56 m
20	2.00 m	–	1.93 m	1.77 m
21β	2.78 t (12)	5.85 s	2.18 t (13)	2.54 m
21α	3.41 dd (12, 5.6)		2.92 dd (13, 3)	3.21 m
22b	3.01 d (10)	3.00 m	2.48 d (11)	2.50 m
22a	4.59 d (10)	4.21 d (11)	4.11 d (9)	3.40 dd (13, 11)
NH	–	–	4.85 br s	–
2'	–	–	–	4.12 d (5)
3'	3.80 br s	3.76 br s	3.72 br s	3.02 br s
5'β	2.78 dd (12, 7.6)	2.80 m	2.76 dd (12, 8)	2.92 m
5'α	2.98 m	3.05 m	3.01 m	3.09 m
6'α	1.50 m	1.49 m	1.82 m	2.26 m
6'β	2.57 td (12, 5)	2.01 m	2.62 dd (13, 4)	2.26 m
9'	7.08 dd (7.3, 1)	7.08 d (7.6)	7.02 d (7)	6.90 d (7.6)
10'	6.83 td (7.3, 1)	6.80 t (7.6)	6.77 t (7.7)	6.70 t (7.6)
11'	7.11 td (7.3, 1)	7.09 t (7.6)	7.10 t (7.7)	6.92 d (7.6)
12'	6.68 dd (7.3, 1)	6.64 d (7.6)	6.54 d (7.2)	–
14'*R*	1.50 m	2.04 m	1.28 dt (12, 3)	1.86 m
14'*S*	2.03 m	2.67 m	1.85 m	2.35 dt (13, 3)
15'	2.33 br s	2.32 br s	1.93 m	2.82 m
18'	0.99 t (7.3)	1.00 t (7.3)	0.53 t (7)	1.00 t (7.3)
19'	1.75 m	1.63 m	–0.13 m	1.26 m
	1.75 m	1.68 m	–0.11 m	1.43 m
20'	1.77 m	1.78 m	1.41 m	1.72 m
21'β	2.62 t (12)	2.57 t (12)	1.72 t (12)	2.13 t (12)
21'α	3.01 m	3.00 m	2.69 dd (12, 4)	2.70 dd (12, 4)
22'b	2.03 m	1.97 m	1.98 d (14)	5.06 s
22'a	2.91 d (13)	2.93 d (12)	2.52 d (16)	5.40 s
NH'	–	–	–	6.85 d (5)

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HSQC, and HETCOR.

Table 2.28: ^{13}C NMR Spectroscopic Data of Leucoridines A–D (**39**–**42**)[a]

C	**39**	**40**	**41**	**42**
2	188.0	187.9	215.7	192.7
3	69.5	66.6	64.7	70.9
5	58.0	55.0	52.7	57.6
6	35.0	40.5	36.5	33.0
7	65.6	65.7	60.6	66.4
8	146.5	147.0	124.8	145.2
9	120.4	120.2	125.1	121.0
10	125.6	125.8	118.1	125.4
11	127.4	127.6	128.5	127.6
12	119.8	120.3	117.6	119.5
13	153.7	154.7	147.5	153.7
14	30.1	27.1	28.0	28.5
15	42.4	42.3	47.7	41.8
16	47.7	47.5	52.4	40.5
18	12.9	13.0	14.2	11.4
19	27.4	29.4	27.5	24.8
20	44.6	124.1	46.1	42.4
21	53.6	131.9	51.8	51.5
22	49.4	50.3	50.5	35.0
2'	147.8	148.2	149.4	71.1
3'	61.5	61.7	61.8	67.1
5'	53.6	53.9	53.7	55.2
6'	40.0	31.8	40.7	41.2
7'	50.6	51.1	51.3	53.9
8'	136.9	137.1	135.3	137.7
9'	119.9	119.7	119.7	120.1
10'	120.4	120.4	119.9	118.9
11'	126.8	126.9	127.5	128.6
12'	108.9	108.8	108.1	122.4
13'	150.0	150.2	148.8	149.4
14'	31.5	37.5	32.0	26.9
15'	34.1	34.8	34.7	33.7
16'	110.2	108.8	101.7	146.9
18'	11.8	12.0	12.8	11.7
19'	25.3	25.6	24.6	24.1
20'	39.7	40.0	39.0	43.3
21'	51.5	51.9	52.0	50.7
22'	46.3	45.4	40.0	115.7

[a] $CDCl_3$, 100 MHz; assignments based on HMQC, HSQC, HETCOR, and HMBC.

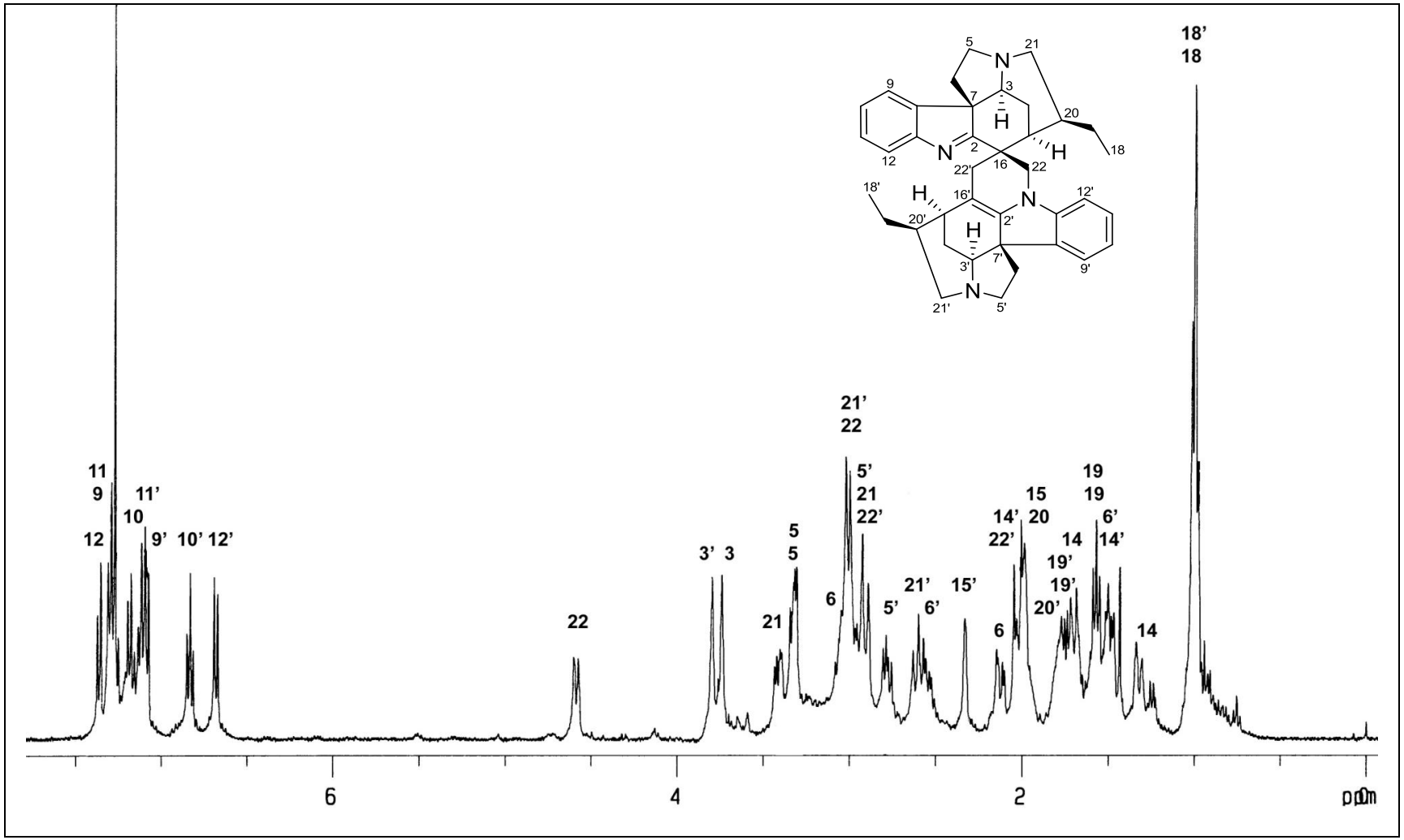


Figure 2.62: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leucoridine A (**39**)

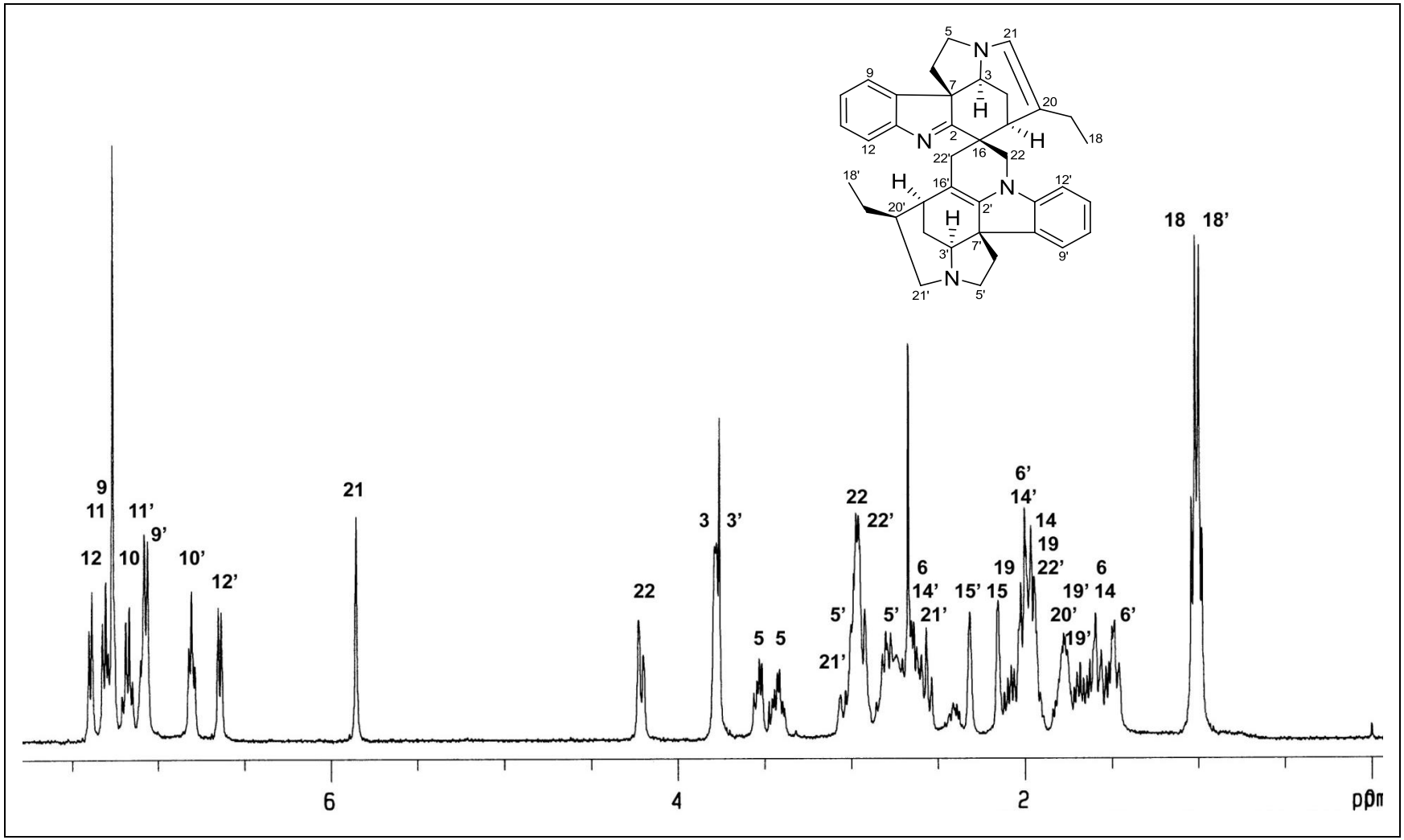


Figure 2.63: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leucoridine B (**40**)

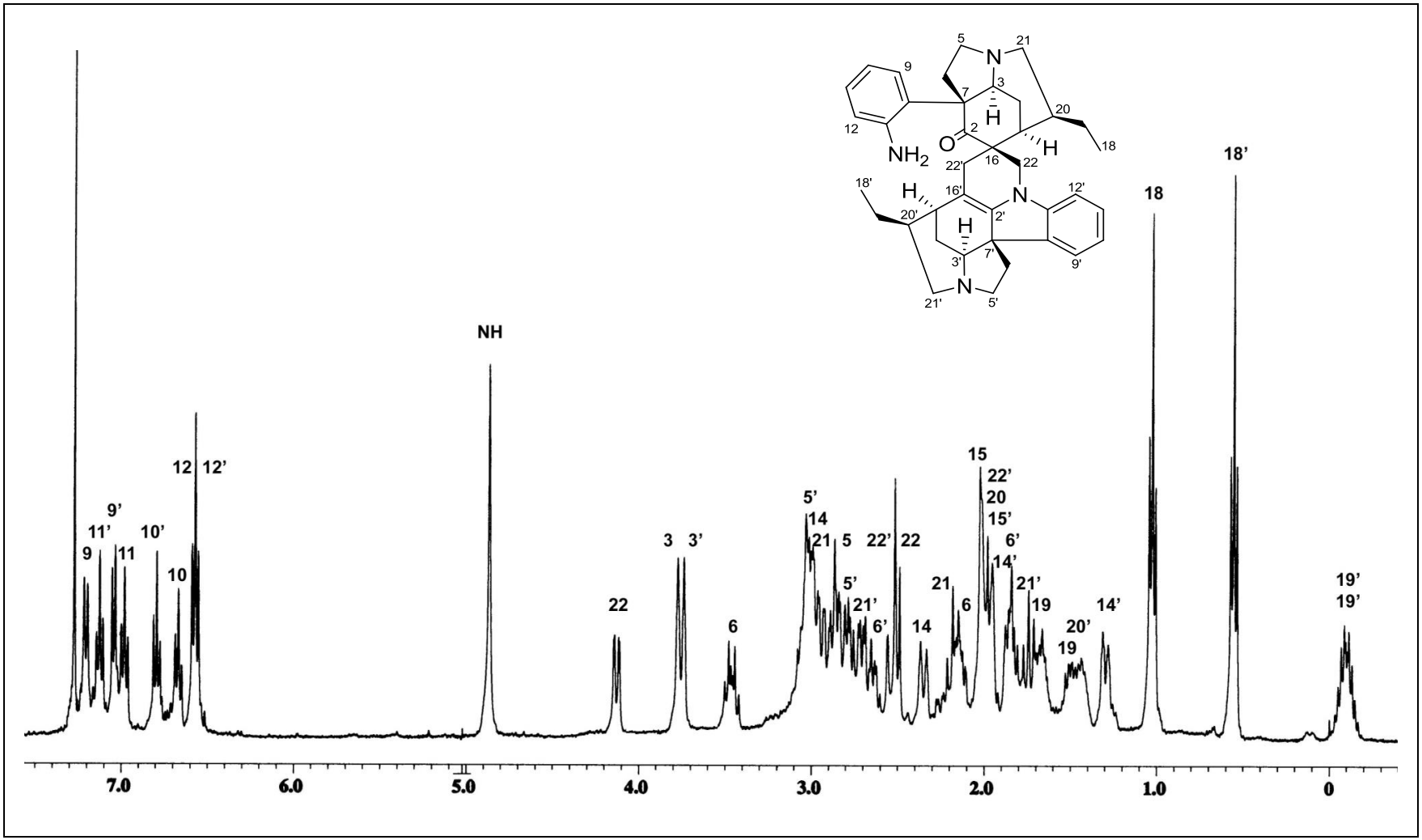


Figure 2.64: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leucoridine C (**41**)

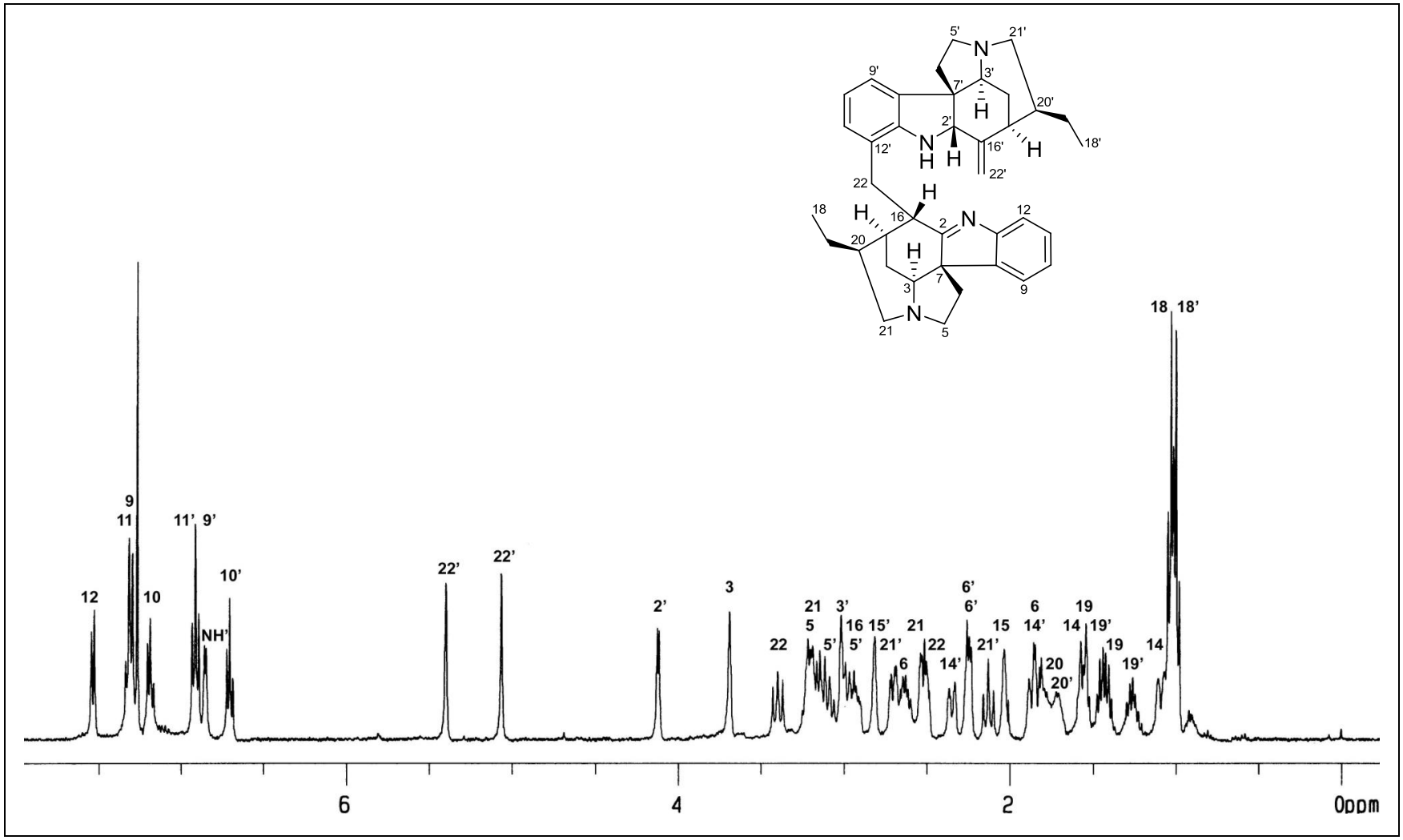


Figure 2.65: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of leucoridine D (**42**)

2.1.6 Corynanthe Alkaloids

2.1.6.1 Tetrahydroalstonine (43), 17(*S*)-Ajmalicinial (44), 17(*R*)-Ajmalicinial (45), Akuammidine (46), 16(*R*)-19,20-*E*-Isositsirikine (47), 16(*S*)-19,20-*E*-Isositsirikine (48), *Z*-Geissoschizol (49), Pleiocarpamine (50), 16-Hydroxymethylpleiocarpamine (51), Fluorocarpamine (52), (–)-Isovallesiachotamine (53), and (+)-Vallesiachotamine (54)

Twelve known alkaloids belonging to this group, *viz.*, tetrahydroalstonine (**43**),[188] 17(*S*)-ajmalicinial (**44**),[333] 17(*R*)-ajmalicinial (**45**),[333] akuammidine (**46**),[334] 16(*R*)-19,20-*E*-isositsirikine (**47**),[335-337] 16(*S*)-19,20-*E*-isositsirikine (**48**),[335-337] *Z*-geissoschizol (**49**),[338,339] pleiocarpamine (**50**),[188,193,340] 16-hydroxymethylpleiocarpamine (**51**),[188,193] fluorocarpamine (**52**),[341,342] (–)-isovallesiachotamine (**53**),[343,344] and (+)-vallesiachotamine (**54**)[340,343,344] were isolated. 17(*S*)-ajmalicinial (**44**) and 17(*R*)-ajmalicinial (**45**) were obtained as an inseparable mixture of isomers at C(17), while (–)-isovallesiachotamine (**53**) and (+)-vallesiachotamine (**54**) were obtained as a pair of inseparable *Z*/*E* isomers with respect to the C(19)–C(20) double bond. However, the thermodynamically more stable isomer, (–)-isovallesiachotamine (**53**) was also obtained. The ^{1}H NMR spectra of these compounds are shown in Figures 2.66–2.76, while the NMR spectroscopic data are summarized in Tables 2.29–2.35. Other data are given in the Experimental Section.

Table 2.29: ^{1}H NMR Spectroscopic Data of Tetrahydroalstonine (**43**), 17(*S*)-Ajmalicinial (**44**), and 17(*R*)-Ajmalicinial (**45**)[a]

H	**43**	**44**	H	**45**
3	3.35 dd (12, 2)	3.24 d (10)	3′	3.32 d (10)
5	2.55 m	2.64 td (11.3, 5)	5′	2.64 td (11.3, 5)
	2.93 m	3.08 m		3.08 m
6	2.69 m	2.73 br d (16)	6′	2.73 br d (16)
	2.93 m	3.08 m		3.08 m
9	7.27 d (7.5)	7.46 br d (7.2)	9′	7.46 br d (7.2)
10	7.07 td (7.5, 1.5)	7.07 td (7.2, 1)	10′	7.07 td (7.2, 1)
11	7.12 td (7.5, 1.5)	7.11 td (7.2, 1)	11′	7.11 td (7.2, 1)
12	7.45 d (7.5)	7.29 br d (7.2)	12′	7.29 br d (7.2)
14	1.53 q (12)	1.31 m	14′	1.31 m
	2.50 m	1.99 m		1.99 m
15	2.76 m	1.36 m	15′	1.92 m
16	–	1.20 m	16′	1.50 m
		1.83 d (12)		1.74 dd (14, 3)
17	7.56 s	4.73 dd (9.5, 1.8)	17′	5.29 d (2.3)
18	1.40 d (6.2)	1.23 d (6)	18′	1.16 d (6)
19	4.50 dq (10.3, 6.2)	3.32 m	19′	3.88 dq (15.8, 6)
20	1.69 m	1.36 m	20′	1.50 m
21	2.73 dd (12.3, 2)	1.99 m	21′	2.10 t (11.3)
	3.10 dd (12.3, 3.5)	2.95 br d (12)		2.95 br d (12)
NH	7.87 s	8.66 br s	NH′	8.66 br s
CO_2Me	3.75 s	–		

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

Table 2.30: ^{13}C NMR Spectroscopic Data of Tetrahydroalstonine (**43**), 17(*S*)-Ajmalicinial (**44**), and 17(*R*)-Ajmalicinial (**45**)[a]

C	**43**	**44**	C	**45**
2	134.5	134.4	2′	134.4
3	59.8	60.0	3′	60.0
5	53.5	53.5	5′	53.4
6	21.7	21.6	6′	21.6
7	108.0	107.7	7′	107.7
8	127.2	127.3	8′	127.2
9	118.0	118.2	9′	118.2
10	114.4	119.3	10′	119.3
11	121.4	121.4	11′	121.3
12	110.8	111.1	12′	111.1
13	136.0	136.3	13′	136.2
14	34.2	35.5	14′	35.3
15	31.3	38.1	15′	32.6
16	109.5	39.2	16′	36.6
17	155.7	95.6	17′	91.6
18	18.5	19.0	18′	19.0
19	72.5	73.9	19′	67.3
20	38.4	45.7	20′	46.4
21	36.3	56.6	21′	56.6
CO_2*Me*	51.1	–		
CO_2Me	168.0	–		

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

Table 2.31: ^{1}H NMR Spectroscopic Data of Akuammidine (**46**), 16(*R*)-19,20-*E*-Isositsirikine (**47**), and 16(*S*)-19,20-*E*-Isositsirikine (**48**)[a]

H	**46**	**47**	**48**
3	4.28 br d (10)	4.33 br s	3.90 br s
5	2.97 d (5)	3.15 m	2.82 td (12, 4)
		3.27 ddd (13, 6, 2)	3.16 dd (5.5, 1)
6	3.08 br d (15.5)	2.67 dd (16, 6)	2.68 br d (15)
	3.31 dd (15.5, 1.7)	2.99 m	3.00 m
9	7.28 br d (7.7)	7.47 br d (8)	7.48 d (7.6)
10	7.05 td (7.7, 1)	7.10 td (8, 1)	7.09 t (7.6)
11	7.11 td (7.7, 1)	7.16 td (8, 1)	7.14 t (7.6)
12	7.42 br d (7.7)	7.39 br d (8)	7.30 (7.6)
14	1.88 ddd (13, 10, 1.5)	2.24 m	2.25 m
	2.68 ddd (13, 4.6, 1.5)	2.24 m	2.27 m
15	3.06 dd (4.6, 1.5)	3.15 m	3.41 m
16	–	2.52 ddd (11, 8, 5)	2.66 m
17	3.66 d (10.5)	3.54 m	3.87 m
	3.82 d (10.5)	3.54 m	3.92 m
18	1.65 dt (7, 1.8)	1.66 dd (7, 2)	1.62 dd (6.8, 1.7)
19	5.40 q (7)	5.65 br q (7)	5.52 q (6.8)
21	3.60 m	2.98 d (13)	3.08 br d (13)
	3.60 m	3.54 m	3.80 br d (13)
NH	7.67 br s	8.81 s	8.23 br s
CO_2Me	2.94 s	3.81 s	3.59 s

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

Table 2.32: ^{13}C NMR Spectroscopic Data of Akuammidine (**46**), 16(*R*)-19,20-*E*-Isositsirikine (**47**), and 16(*S*)-19,20-*E*-Isositsirikine (**48**)[a]

C	**46**	**47**	**48**
2	136.5	133.8	134.2
3	50.5	52.8	53.3
5	57.7	51.3	51.3
6	24.2	17.7	19.2
7	105.2	107.7	107.8
8	126.4	127.6	127.3
9	117.7	118.0	118.0
10	118.9	119.5	119.3
11	121.2	121.6	121.4
12	110.9	111.3	110.9
13	136.6	136.2	136.2
14	28.8	30.2	30.1
15	28.9	32.6	32.8
16	51.2	49.6	49.7
17	68.1	62.1	61.6
18	12.7	13.3	12.9
19	117.4	123.7	121.8
20	136.8	133.7	134.8
21	54.9	52.5	55.9
CO_2*Me*	51.2	52.2	51.5
CO_2Me	173.6	175.4	174.7

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

Table 2.33: ^{1}H and ^{13}C NMR Spectroscopic Data of *Z*-Geissoschizol (**49**) and Fluorocarpamine (**50**)[a]

Position	**49**		**50**	
	δ_H	δ_C	δ_H	δ_C
2	–	134.5	–	76.0
3	3.45 d (11.4)	60.0	3.51 br s	61.8
5	2.62 td (11, 4.5)	52.3	2.99 m	55.0
	3.09 ddd (11.3, 5.9, 2)		2.99 m	
6	2.74 m	21.4	2.21 dd (12, 6)	39.0
	2.95 m		2.99 m	
7	–	107.0	–	205.2
8	–	127.0	–	120.4
9	7.27 br d (7.7)	118.0	7.62 br d (8)	124.1
10	7.01 td (7.7, 1)	119.1	6.90 br t (8)	119.5
11	7.06 td (7.7, 1)	121.2	7.51 br t (8)	137.2
12	7.39 br d (7.7)	111.1	6.70 br d (8)	111.1
13	–	136.3	–	163.6
14	1.20 m	35.8	1.37 dt (13, 3)	24.9
	2.32 dt (12.7, 3.4)		1.91 dt (13, 3)	
15	2.26 m	37.9	3.64 br d (9)	30.5
16	1.44 ddt (14, 8, 5.9)	33.8	4.56 d (9)	63.0
	1.93 ddd (14, 11.8, 7)			
17	3.69 t (5.9)	60.0	–	–
	3.69 t (5.9)			
18	1.65 d (7)	13.0	1.63 d (6)	12.3
19	5.27 q (7)	116.9	5.50 br q (6)	121.0
20	–	136.5	–	133.9
21	2.69 d (12)	55.5	3.31 d (14)	53.4
	3.81 d (12)		3.38 br d (14)	
NH	9.24 br s	–	–	–
CO_2*Me*	–	–	3.72 s	51.8
CO_2Me	–	–	–	172.5

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

Table 2.34: ^{1}H and ^{13}C NMR Spectroscopic Data of Pleiocarpamine (**51**) and 16-Hydroxymethylpleiocarpamine (**52**)[a]

Position	**51**		**52**	
	δ_H	δ_C	δ_H	δ_C
2	–	136.2	–	137.1
3	3.87 t (3)	50.6	3.77 m	50.4
5	2.30 ddd (13.3, 8.5, 6.5)	50.0	2.25 ddd (13.3, 8.5, 6.5)	49.5
	3.38 ddd (13.3, 10, 2.8)		3.35 ddd (13.3, 10, 2.8)	
6	2.69 ddd (15.5, 10, 6.5)	20.5	2.63 ddd (15.5, 10, 6.5)	20.5
	3.17 ddd (15.5, 8.5, 2.8)		3.15 ddd (15.5, 8.5, 2.8)	
7	–	108.2	–	108.7
8	–	128.4	–	128.7
9	7.12 m	118.4	7.54 m	118.3
10	6.97 m	120.1	7.10 m	120.2
11	7.08 m	120.9	7.10 m	121.0
12	7.55 m	112.3	7.10 m	112.0
13	–	137.7	–	139.0
14	2.22 ddd (13.5, 4.2, 2.5)	28.0	2.03 ddd (13.5, 4, 2.2)	25.4
	2.51 ddd (13.5, 4, 2.5)		2.62 m	
15	3.53 m	33.5	3.74 t (3.5)	33.3
16	5.23 d (4)	61.1	–	68.5
17	–	–	4.24 d (12)	66.0
			4.52 d (12)	
18	1.49 dd (7, 2)	12.5	1.52 dd (7, 2)	12.5
19	5.33 qd (7, 2)	123.6	5.29 qd (7, 2)	122.2
20	–	132.4	–	134.5
21	1.76 dt (13, 2)	56.4	1.85 dt (13, 2)	56.5
	2.62 d (13)		2.61 d (13)	
CO_2*Me*	3.58 s	51.9	3.32 s	51.5
CO_2Me	–	168.9	–	173.1

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

Table 2.35: ^{1}H and ^{13}C NMR Spectroscopic Data of (–)-Isovallesiachotamine (**53**) and (+)-Vallesiachotamine (**54**)[a]

Position	**53**		Position	**54**	
	δ_H	δ_C		δ_H	δ_C
2	–	132.2	2′	–	132.6
3	4.25 br d (12)	47.7	3′	4.47 br d (12)	49.4
5	3.59 td (12, 5)	50.9	5′	3.59 td (12, 5)	51.0
	3.69 td (12, 5)			3.69 td (12, 5)	
6	2.79 m	21.9	6′	2.79 m	22.1
	2.92 m			2.92 m	
7	–	108.1	7′	–	108.3
8	–	136.3	8′	–	136.4
9	7.46 br d (7)	117.8	9′	7.48 br d (7)	118.1
10	7.10 td (7, 1)	119.4	10′	7.10 td (7, 1)	119.7
11	7.16 td (7, 1)	121.8	11′	7.16 td (7, 1)	122.0
12	7.30 br d (7.8)	111.1	12′	7.30 br d (7.8)	111.2
13	–	126.6	13′	–	126.8
14	1.79 ddd (13, 12, 5.6)	32.6	14′	1.91 ddd (13, 12, 6)	34.1
	2.24 m			2.20 m	
15	4.03 m	30.8	15′	4.02 m	28.6
16	–	93.3	16′	–	94.1
17	7.76 s	147.9	17′	7.68 s	147.7
18	2.19 d (7.6)	13.0	18′	2.10 d (7.3)	15.2
19	6.55 q (7.6)	147.3	19′	6.68 q (7.3)	153.3
20	–	143.1	20′	–	146.5
21-CHO	10.27 s	190.8	21′-CHO	9.36 s	196.2
NH	8.29 br s	–	NH′	8.22 br s	–
CO_2*Me*	3.66 s	50.7	CO_2*Me*′	3.64 s	51.2
CO_2Me	–	168.2	*C*O_2Me′	–	168.6

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

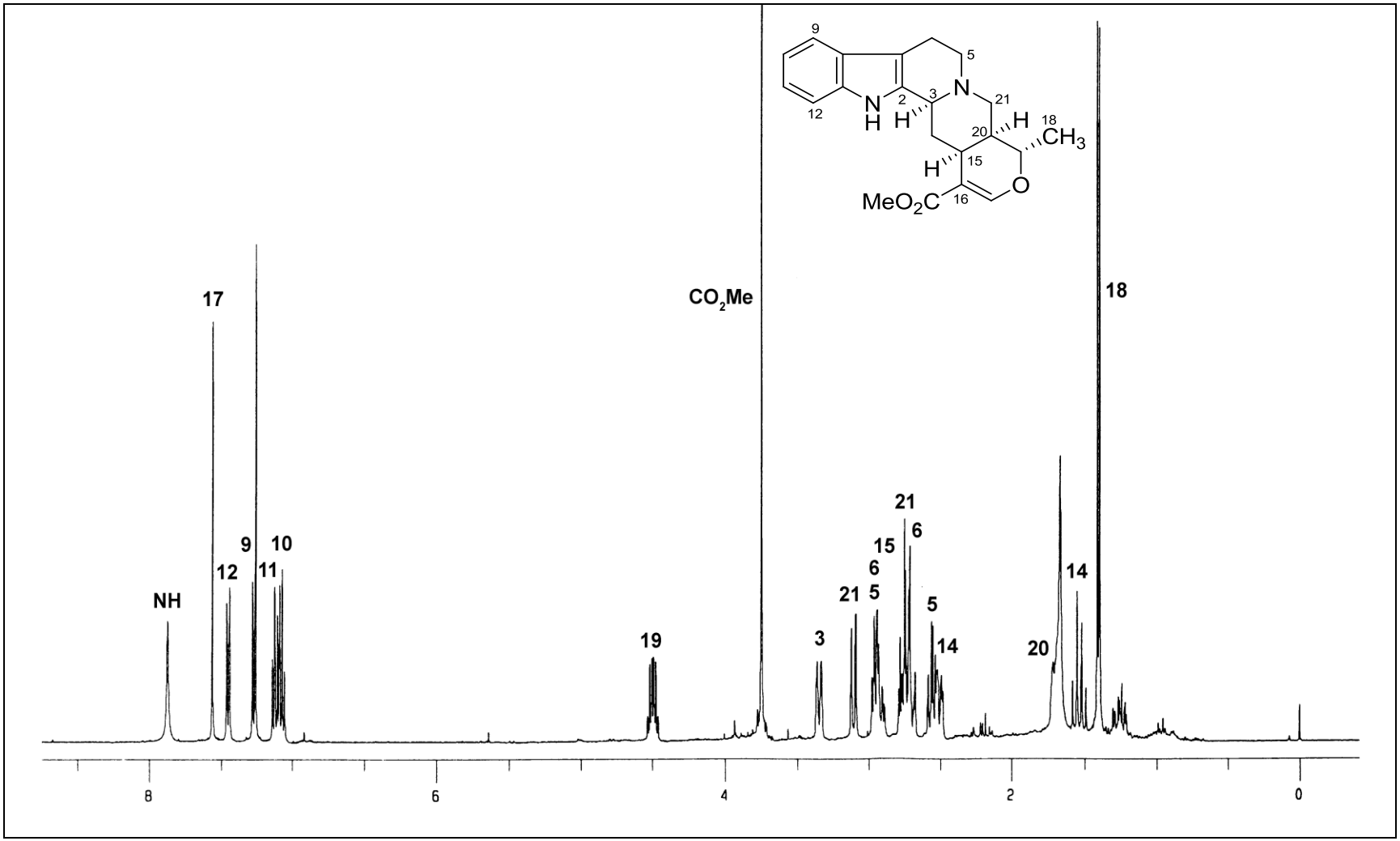


Figure 2.66: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of tetrahydroalstonine (**43**)

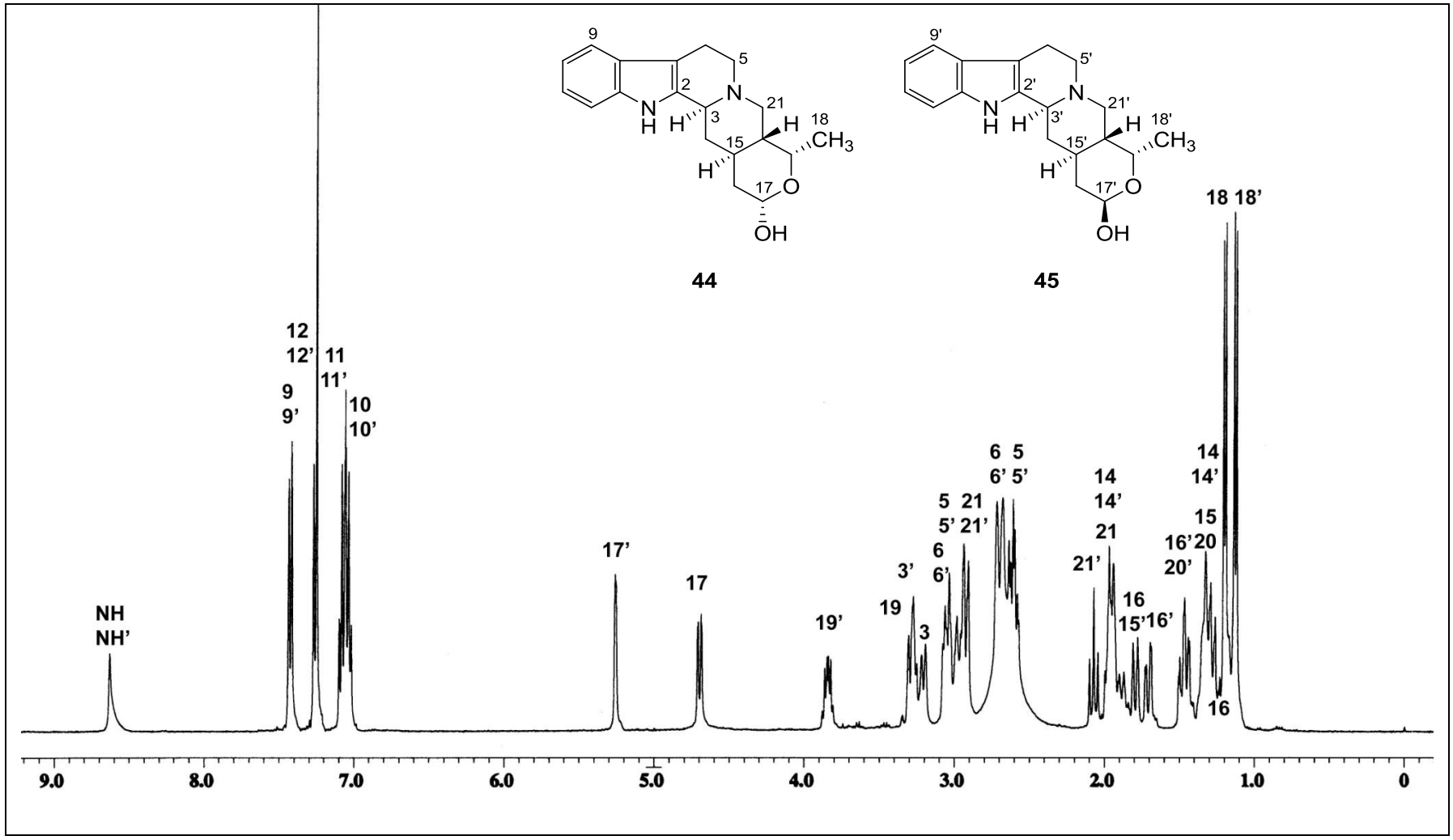


Figure 2.67: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 17(*S*)-ajmalicinial (**44**) and 17(*R*)-ajmalicinial (**45**)

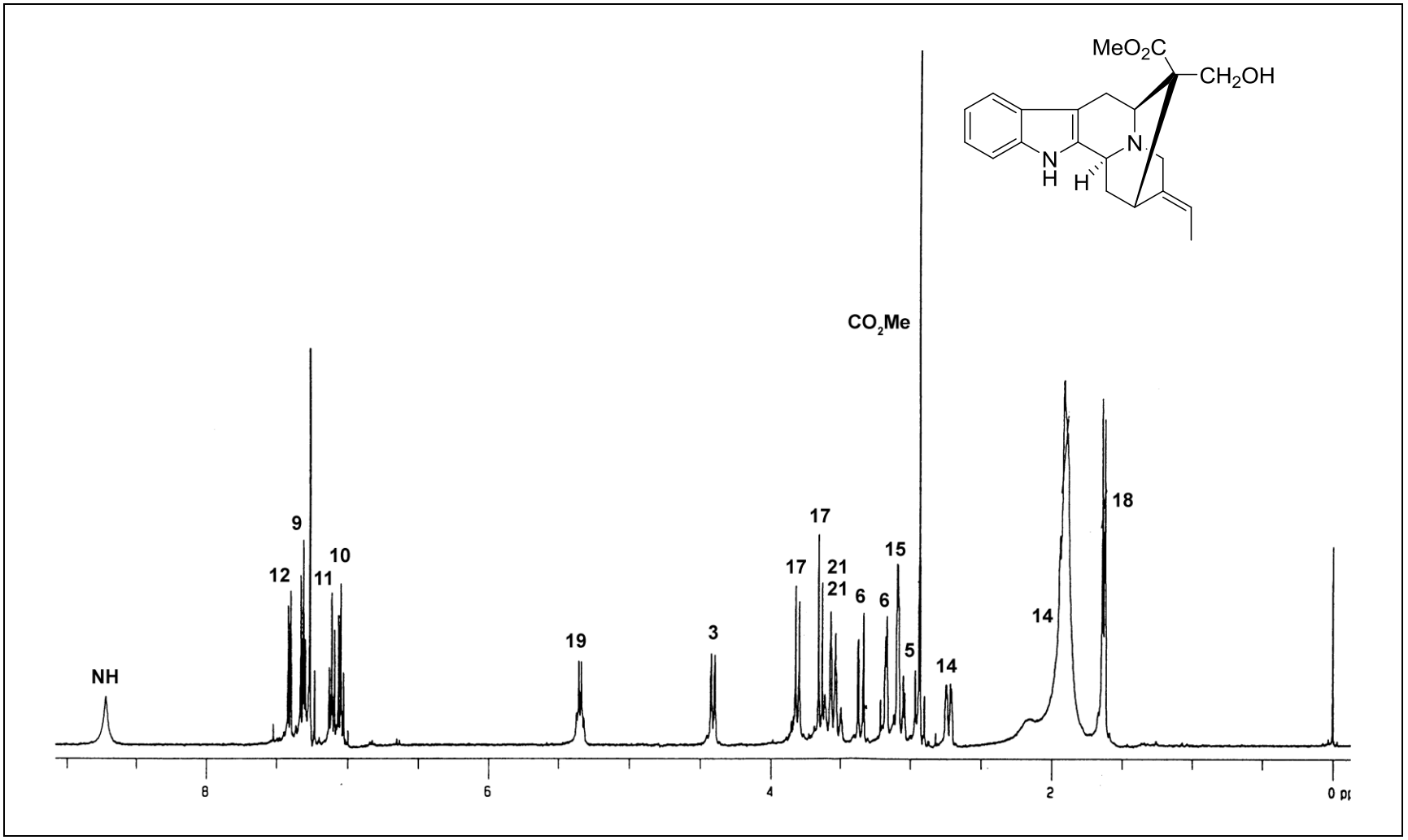


Figure 2.68: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of akuammidine (**46**)

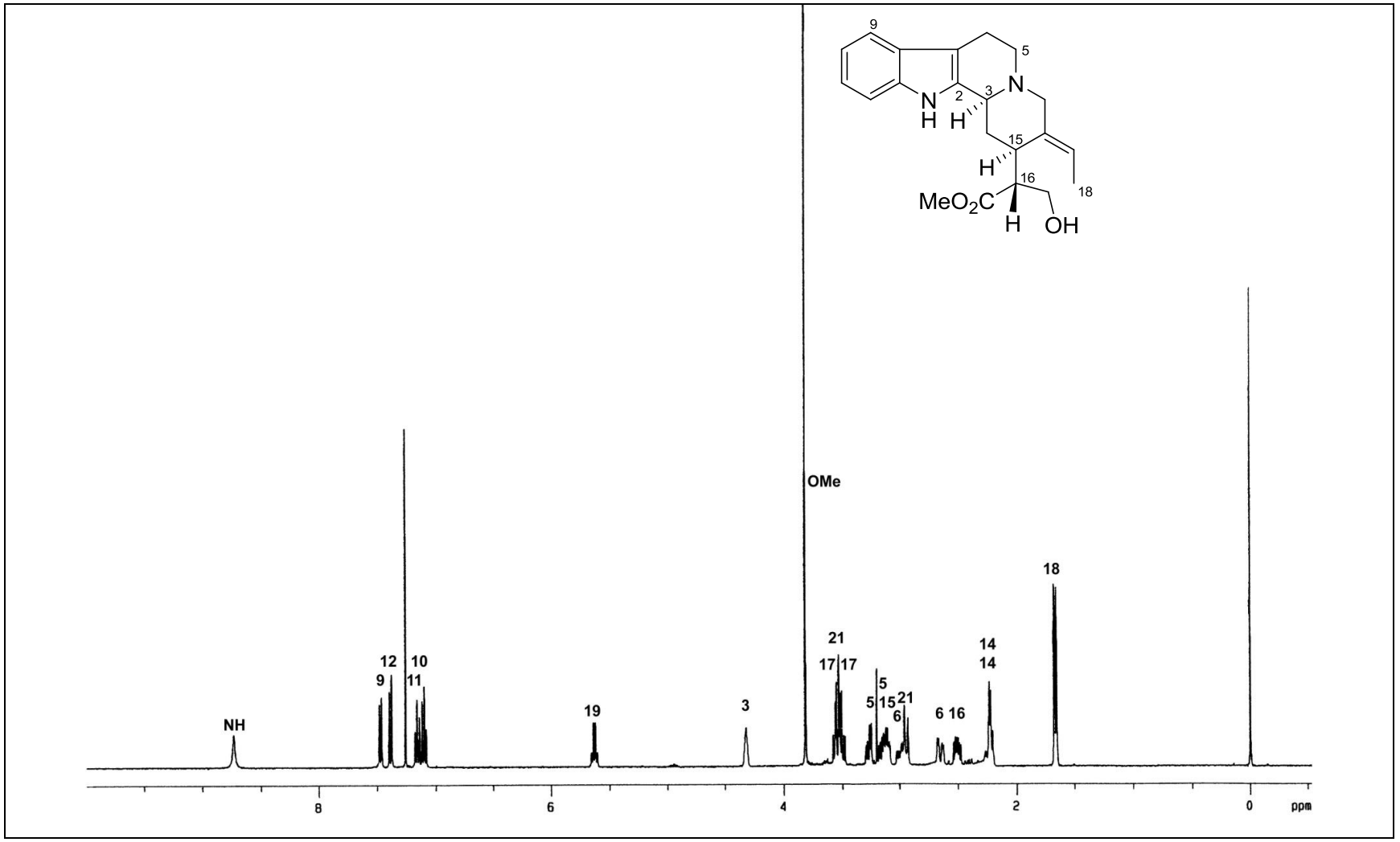


Figure 2.69: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 16(*R*)-19,20-*E*-isositsirikine (**47**)

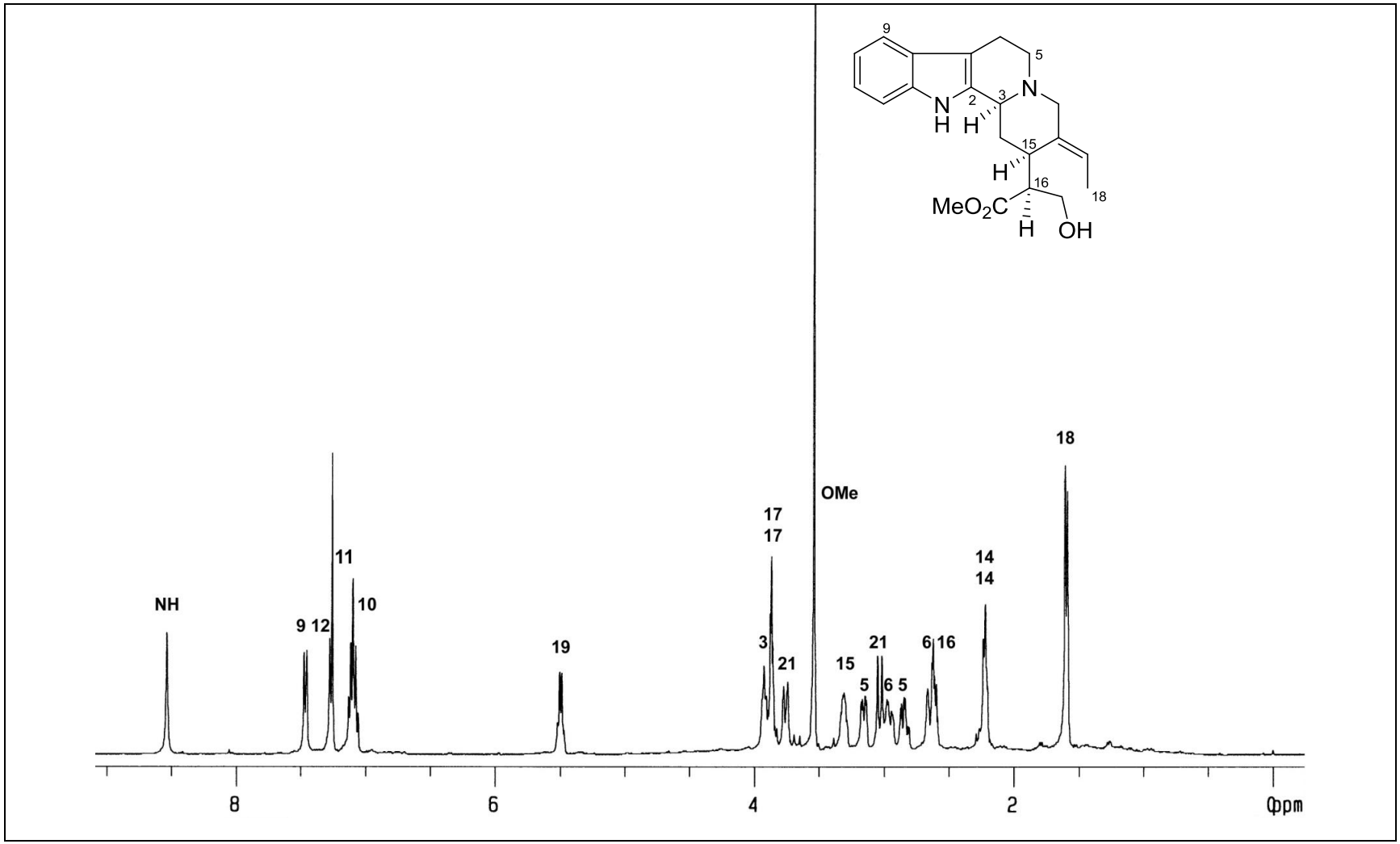


Figure 2.70: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 16(*S*)-19,20-*E*-isositsirikine (**48**)

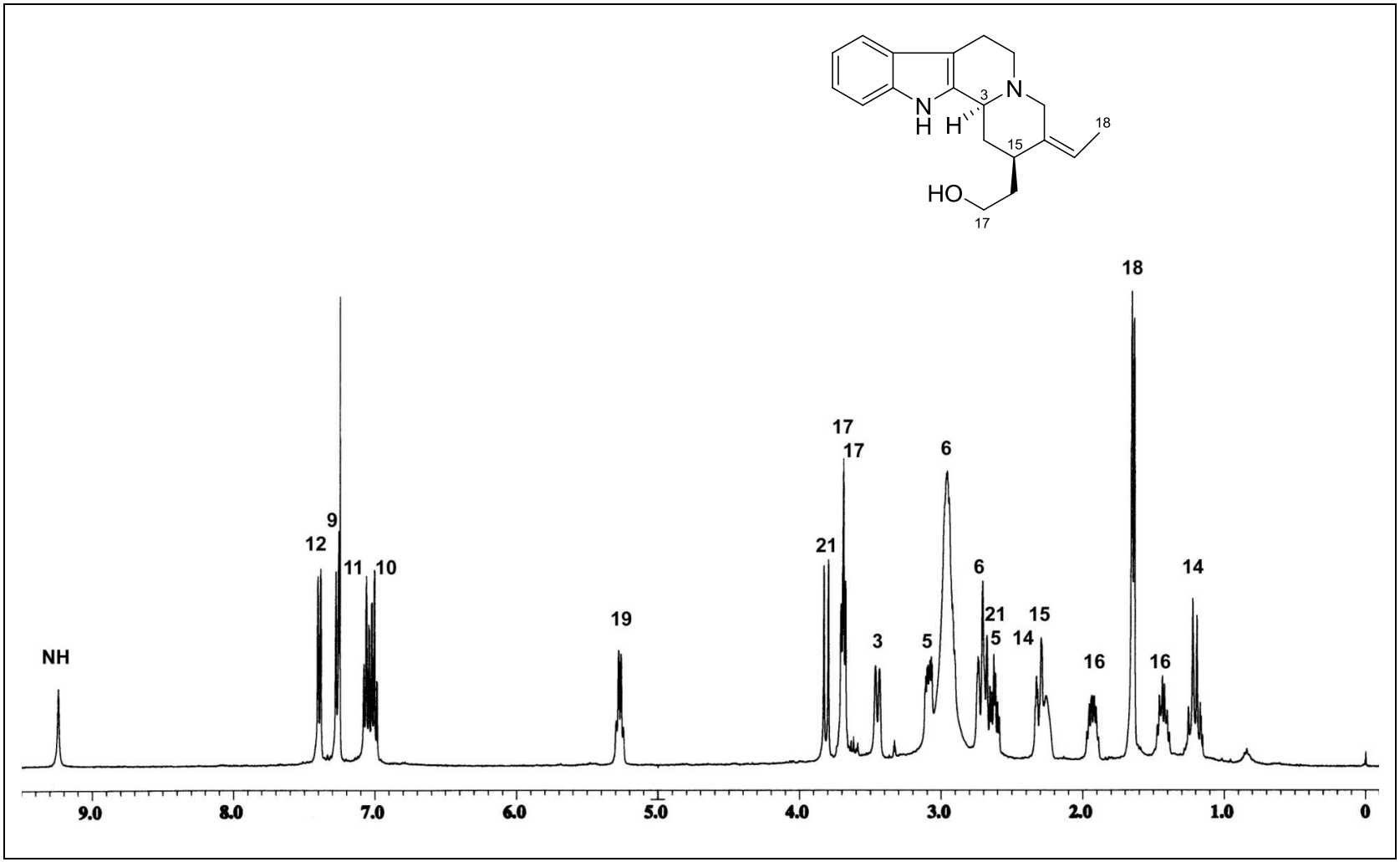


Figure 2.71: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *Z*-geissoschizol (**49**)

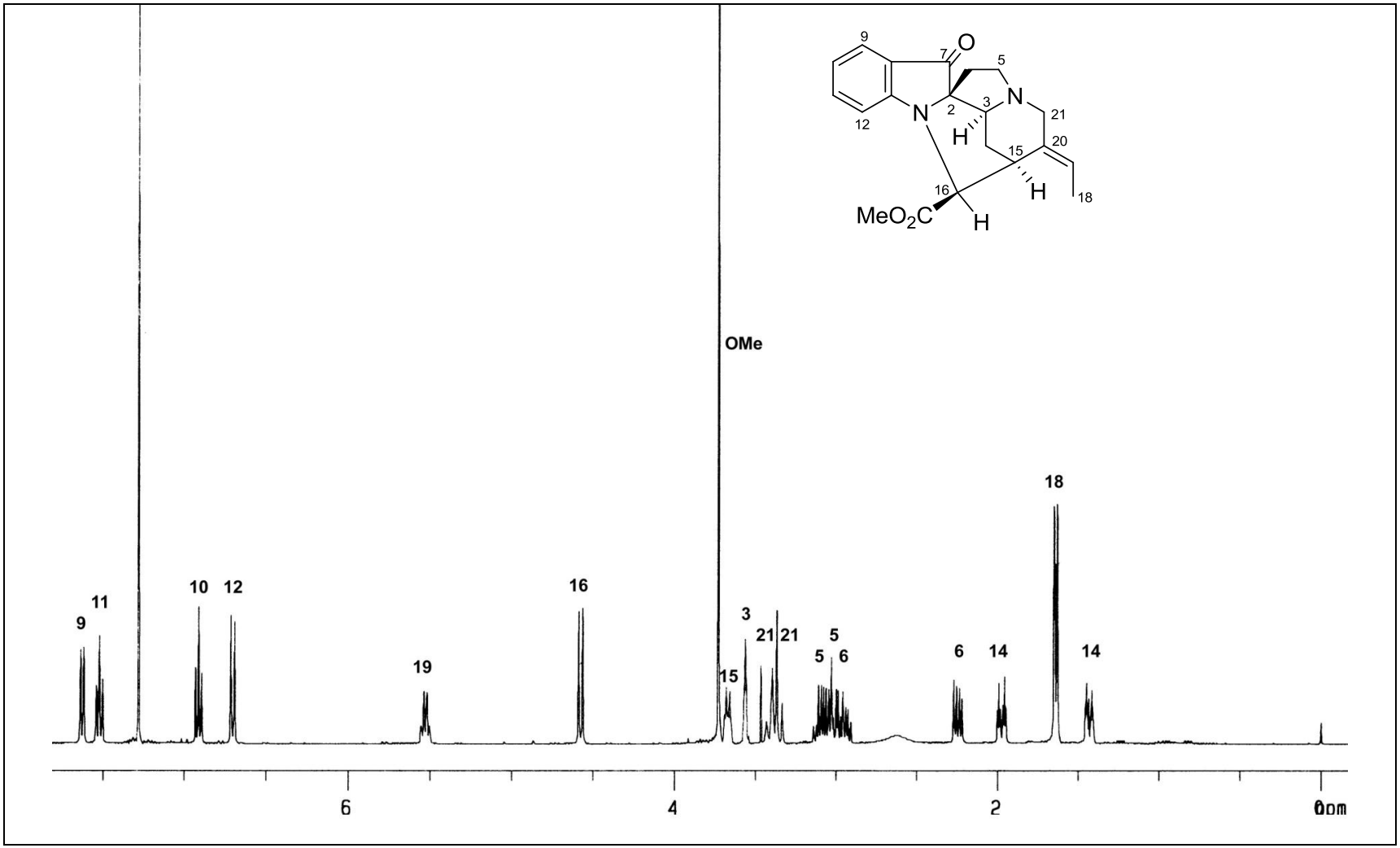


Figure 2.72: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of fluorocarpamine (**50**)

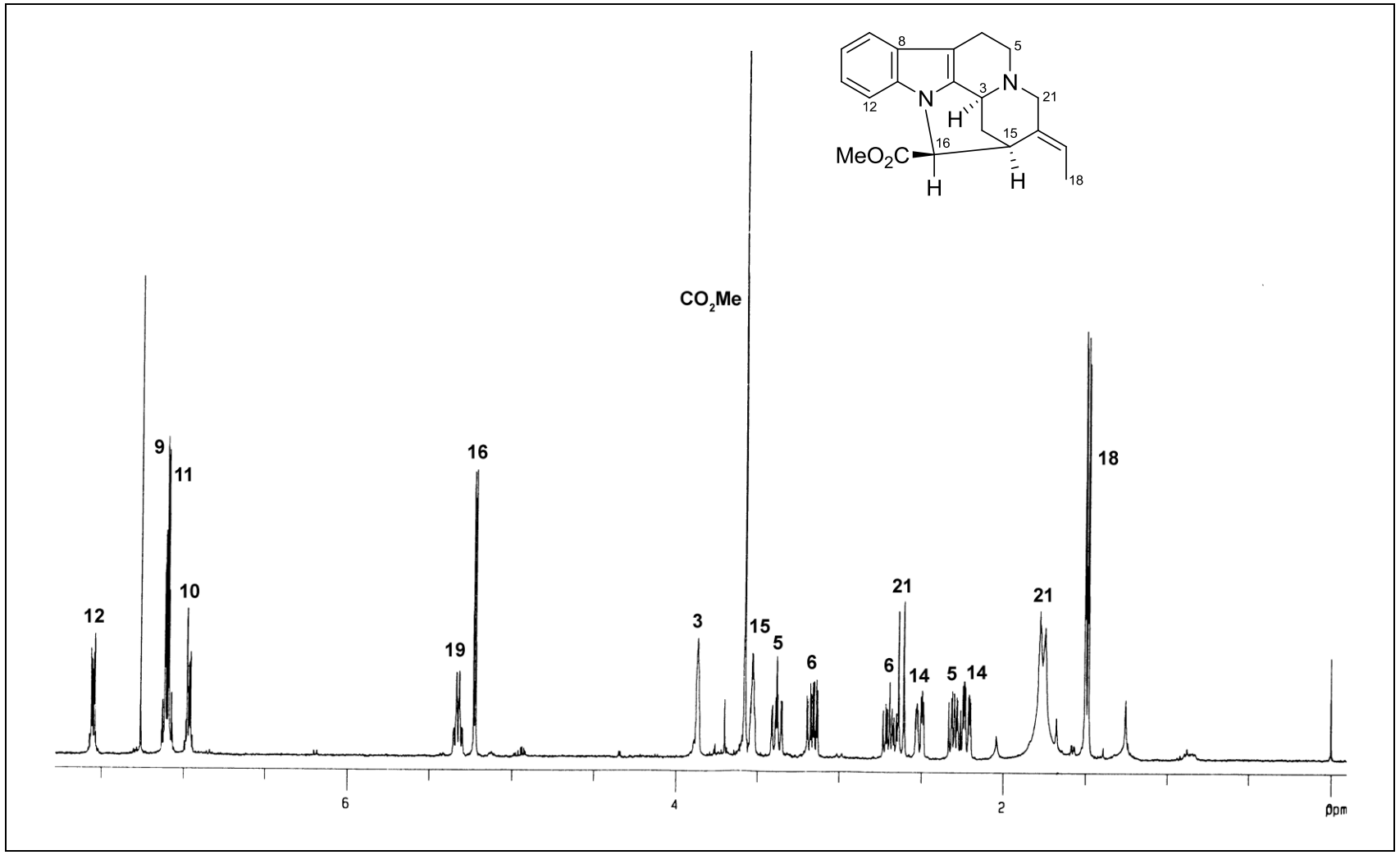


Figure 2.73: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of pleiocarpamine (**51**)

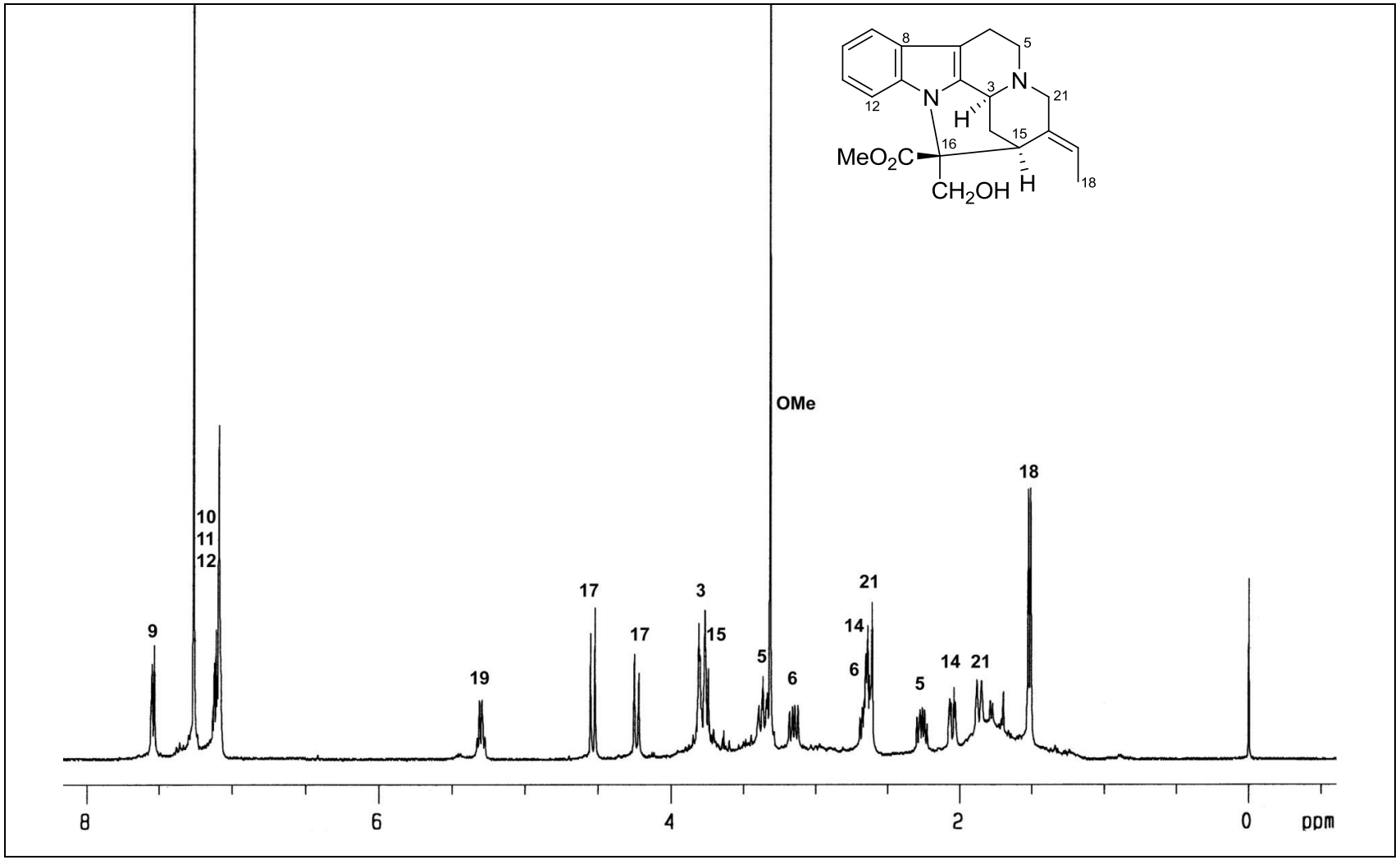


Figure 2.74: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 16-hydroxymethylpleiocarpamine (**52**)

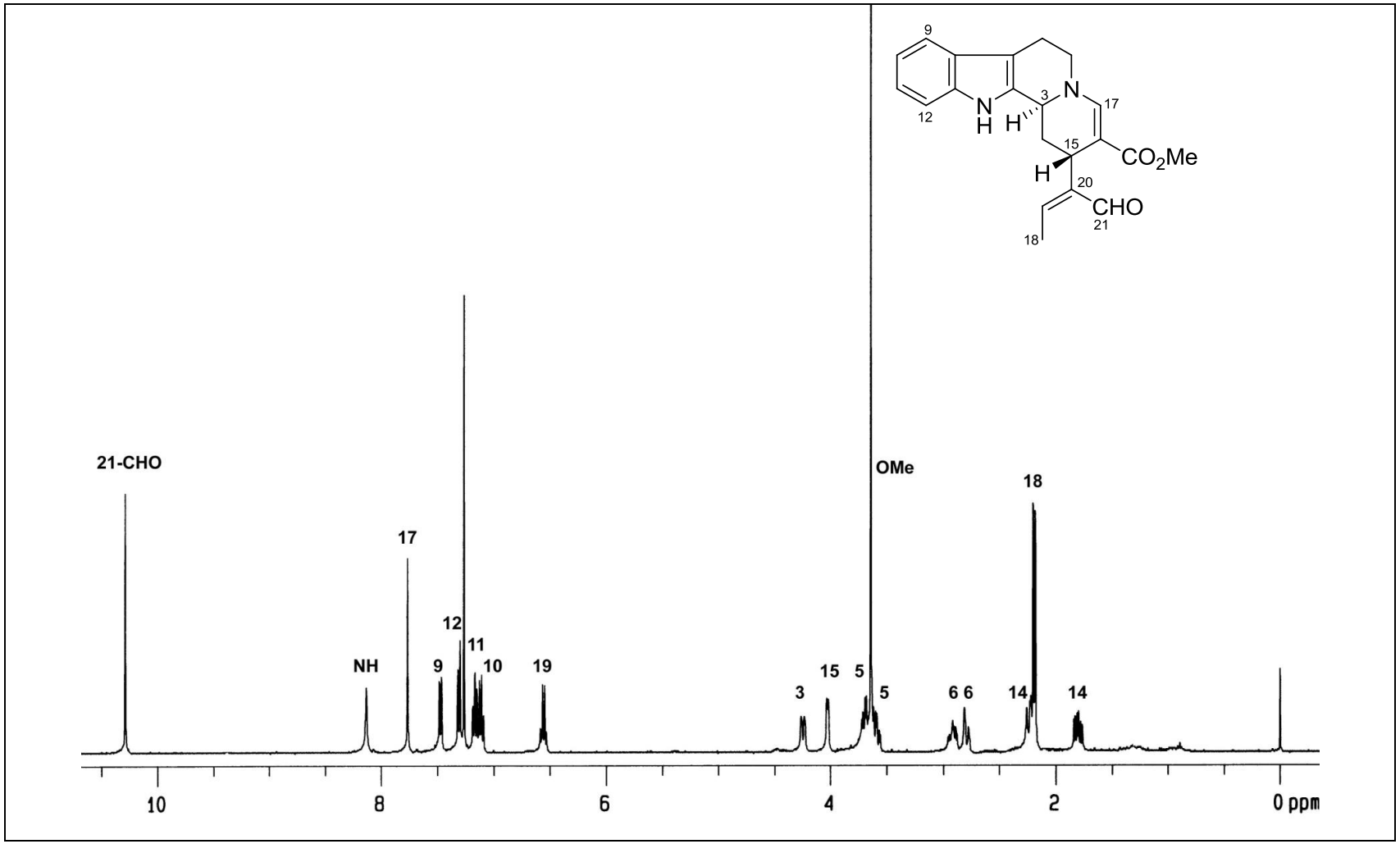


Figure 2.75: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (–)-isovallesiachotamine (**53**)

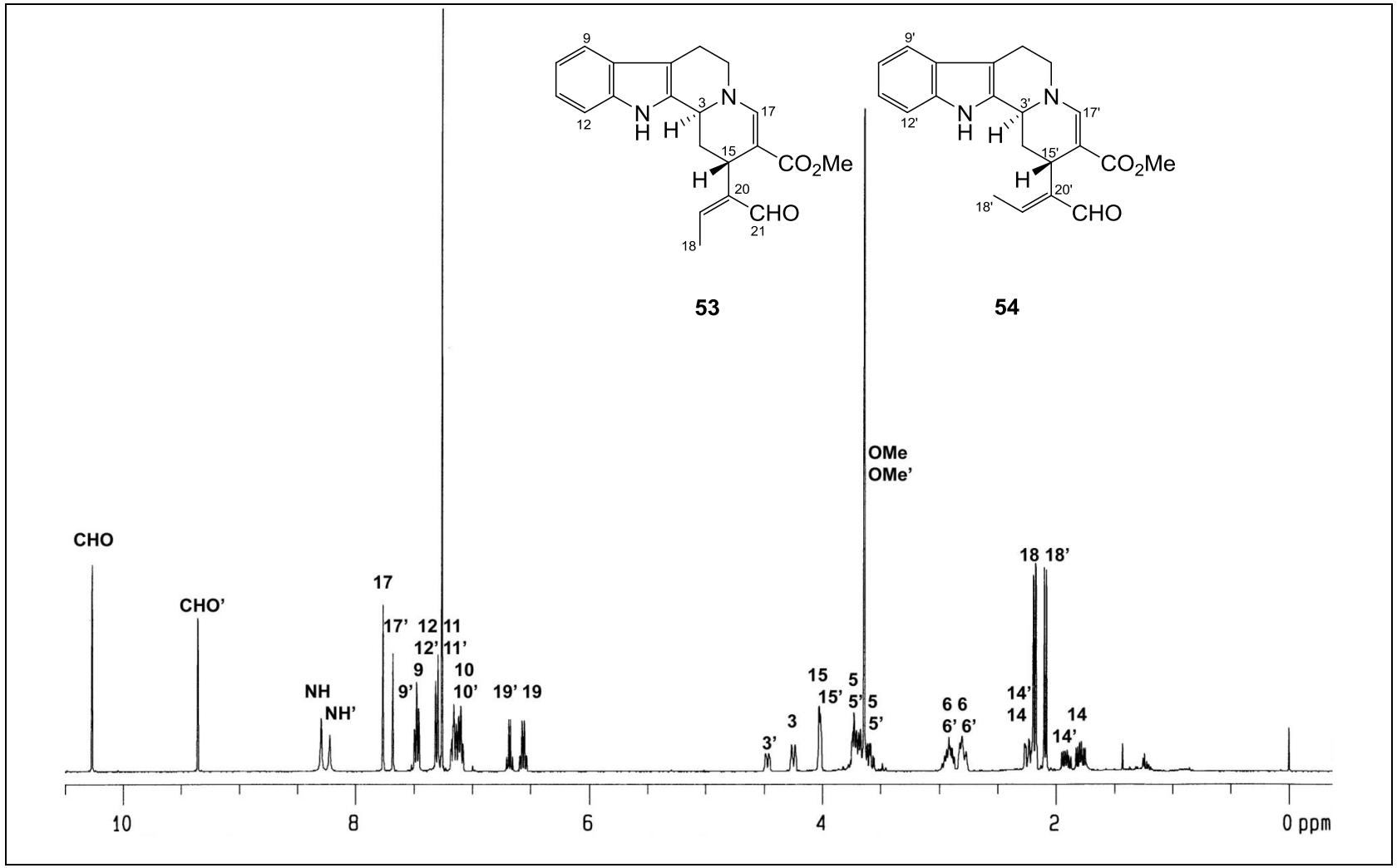


Figure 2.76: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (–)-isovallesiachotamine (**53**) and (+)-vallesiachotamine (**54**)

2.1.7 Norfluorocurarine Alkaloids

2.1.7.1 Norfluorocurarine (55) and 12-Hydroxynorfluorocurarine (56)

Two known alkaloids belonging to this group, *viz.*, norfluorocurarine (**55**)[345] and 12-hydroxynorfluorocurarine (**56**)[345] were also isolated. The ^{1}H NMR spectra of these compounds are shown in Figures 2.77 and 2.78, while the NMR spectroscopic data are summarized in Table 2.36. Other data are given in the Experimental Section.

Table 2.36: ^{1}H and ^{13}C NMR Spectroscopic Data of Norfluorocurarine (**55**) and 12-Hydroxynorfluorocurarine (**56**)[a]

Position	**55**		**56**	
	δ_H	δ_C	δ_H	δ_C
2	–	168.8	–	172.2
3	4.10 td (4, 2)	61.7	4.15 m	62.2
5	3.07 ddd (12.4, 6.5, 1) 3.31 td (12.4, 5.4)	56.6	3.11 br dd (12.6, 6.6) 3.38 td (12.6, 5)	57.0
6	1.83 ddd (12.4, 5.4, 1) 2.39 td (12.4, 6.5)	46.4	1.84 br dd (12.6, 5) 2.47 td (12.6, 6.6)	46.7
7	–	58.2	–	60.1
8	–	136.9	–	139.2
9	7.29 dd (7.5, 1)	120.8	6.86 dd (7.7, 1)	112.1
10	6.98 td (7.5, 1)	121.9	6.98 t (7.7)	124.7
11	7.20 td (7.5, 1)	127.7	6.88 dd (7.7, 1)	116.7
12	6.92 dd (7.5, 1)	110.3	–	143.1
13	–	142.8	–	141.0
14	1.29 ddd (13.5, 4, 2.2) 2.58 ddd (13.5, 4, 2.2)	30.8	1.33 dt (13.5, 3) 2.61 ddd (13.5, 4 , 2)	31.0
15	3.71 m	31.2	3.72 m	32.1
16	–	111.0	–	110.1
17	9.36 s	188.4	9.07 s	186.7
18	1.60 ddd (6.9, 2.3, 1.6)	12.8	1.62 dt (6.9, 2)	13.2
19	5.40 qt (6.9, 2.3)	120.4	5.43 qt (6.9, 2)	121.4
20	–	139.5	–	129.2
21	2.94 br d (15.7) 4.00 dq (15.7, 2.3)	56.7	2.95 br d (15.9) 4.02 dq (15.9, 2)	57.0
NH	10.33 br s	–	11.50 br s	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

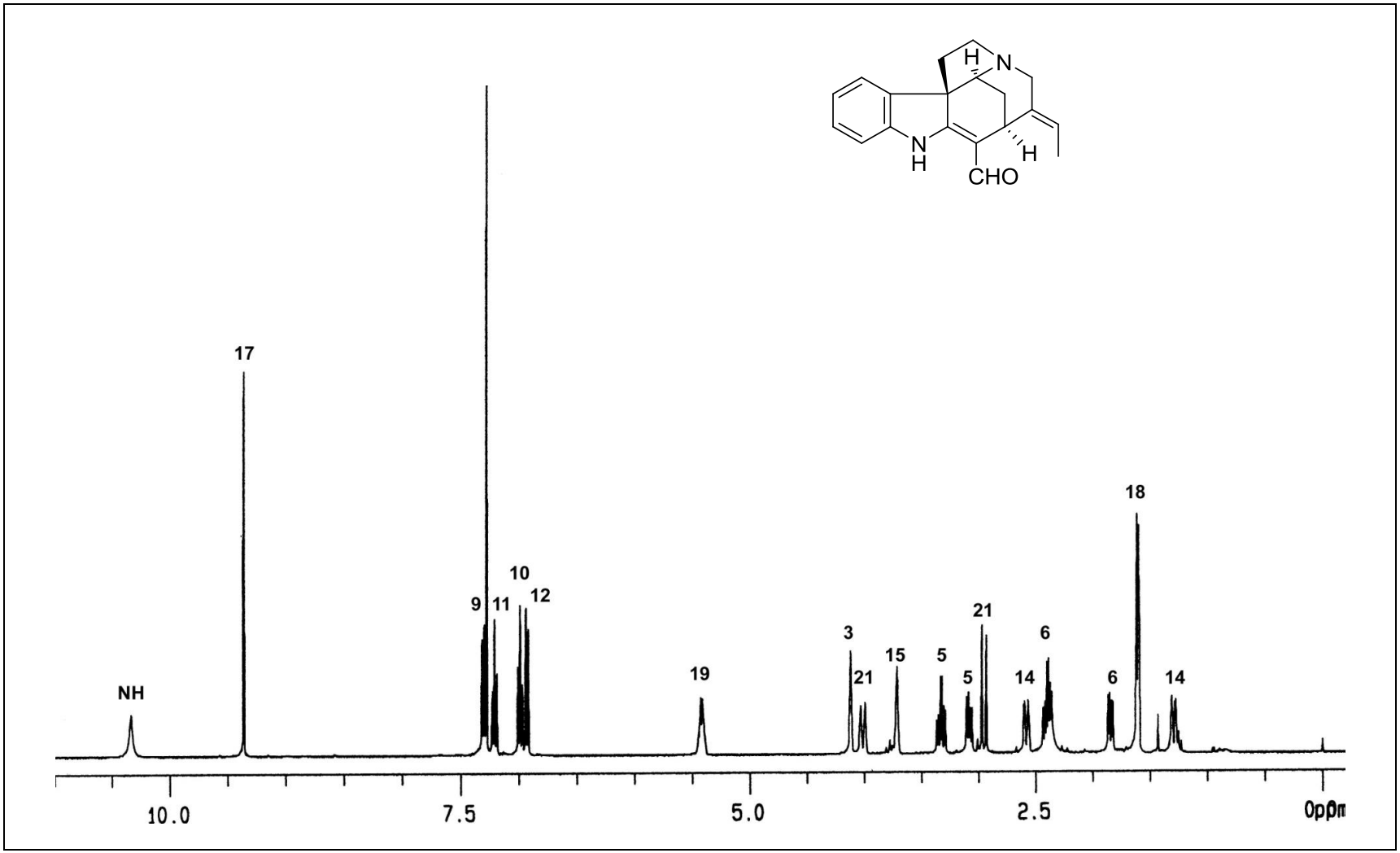


Figure 2.77: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of norfluorocurarine (**55**)

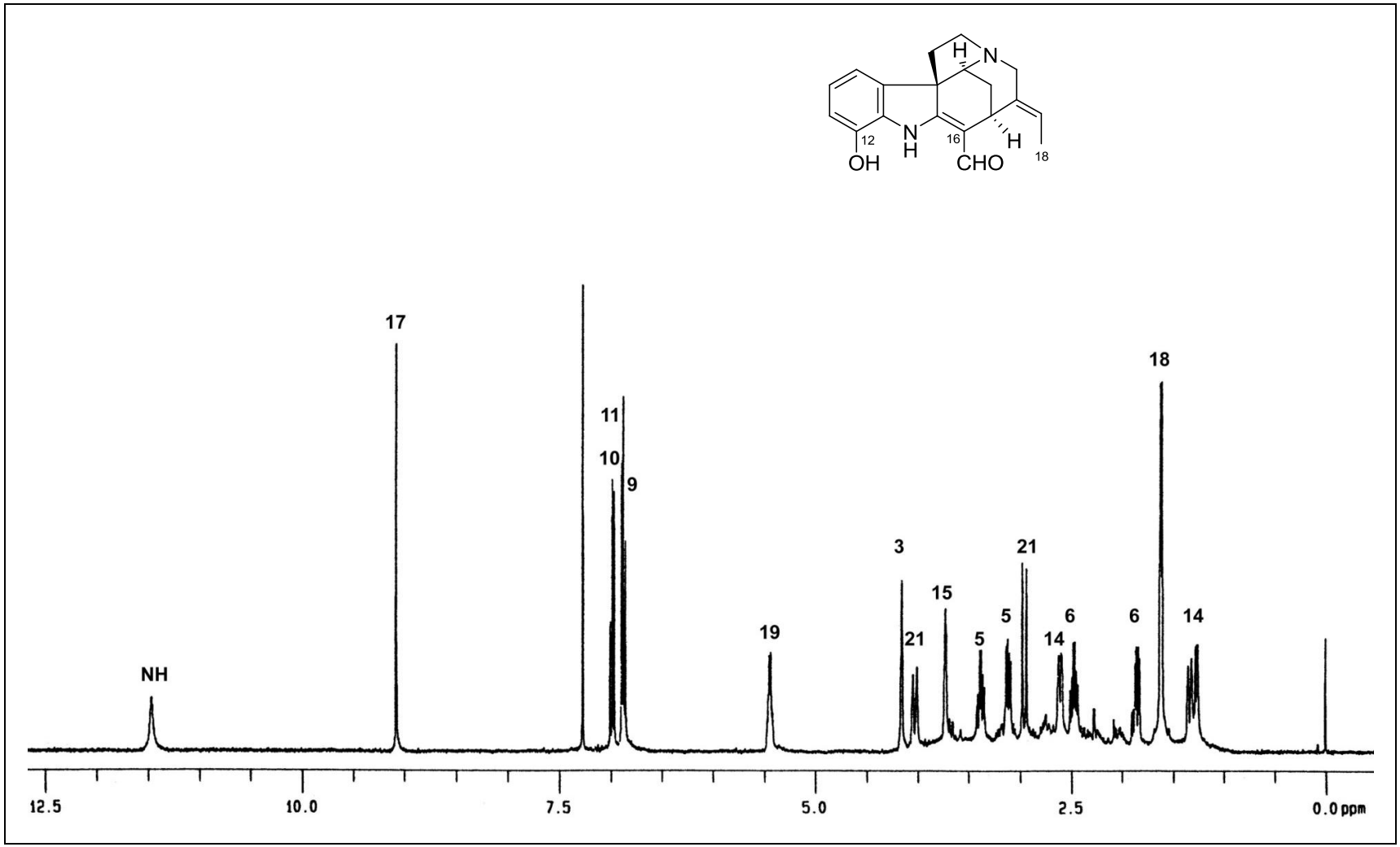


Figure 2.78: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 12-hydroxynorfluorocurarine (**56**)

2.1.8 Aspidospermatan Alkaloids

2.1.8.1 Tubotaiwine (57), Tubotaiwine *N*-oxide (58), and *N*(4)-Chloromethyl-tubotaiwine chloride (59)

Three known alkaloids belonging to this group, *viz.*, tubotaiwine (**57**),[346-348] tubotaiwine *N*-oxide (**58**),[347] and *N*(4)-chloromethyltubotaiwine chloride (**59**)[349] were isolated. The ^{1}H NMR spectra of these compounds are shown in Figures 2.79–2.81, while the NMR data are summarized in Tables 2.37 and 2.38. Other data are given in the Experimental Section.

Table 2.37: ^{1}H NMR Spectroscopic Data of Tubotaiwine (**57**), Tubotaiwine *N*-oxide (**58**), and *N*(4)-Chloromethyltubotaiwine chloride (**59**)[a]

H	**57**	**58**	**59**
3	2.45 dt (12, 9)	3.49 m	3.39 td (14, 4)
	2.95 dt (12, 4)	3.49 m	4.09 dd (14, 4)
5	2.83 dd (10.5, 7)	3.62 dd (11, 8)	3.80 m
	2.89 m	3.73 td (12, 8)	4.44 td (12, 8)
6	1.80 m	2.10 dd (15, 8)	2.26 dd (14, 8)
	2.92 m	2.60 td (14, 8)	2.89 ddd (14, 12, 8)
9	7.13 dd (7.6, 0.5)	7.26 d (7.6)	8.00 br d (7.6)
10	6.87 td (7.6, 0.5)	6.94 t (7.6)	6.99 td (7.6, 1)
11	7.10 td (7.6, 0.5)	7.17 t (7.6)	7.18 td (7.6, 1)
12	6.80 dd (7.6, 0.5)	6.85 d (7.6)	6.87 br d (7.6)
14	1.80 m	1.78 br d (13)	1.98 br d (14)
	1.80 m	2.38 m	2.30 m
15	3.04 m	3.20 m	3.33 m
18	0.70 t (7)	0.73 t (7)	0.77 t (7)
19	0.81 m	0.87 m	0.88 dqu (14, 7)
	0.81 m	0.87 m	1.01 dqu (14, 7)
20	1.96 tt (7, 2.5)	2.51 m	2.30 m
21	3.79 m	4.25 m	5.51 m
22	–	–	5.97 d (10)
			6.60 d (10)
CO_2Me	3.76 s	3.79 s	3.81 s
NH	8.86 s	8.77 s	8.81 s

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

Table 2.38: ^{13}C NMR Spectroscopic Data of Tubotaiwine (**57**), Tubotaiwine *N*-oxide (**58**), and *N*(4)-Chloromethyltubotaiwine chloride (**59**)[a]

C	**57**	**58**	**59**
2	170.8	166.7	166.7
3	45.3	59.9	50.2
5	54.1	67.6	59.5
6	44.1	39.3	38.9
7	55.2	51.3	53.6
8	137.3	134.5	133.2
9	119.6	119.6	121.8
10	121.1	121.9	122.6
11	127.2	128.5	128.7
12	109.7	110.5	110.2
13	143.7	143.1	142.3
14	28.6	24.8	24.4
15	31.0	29.6	29.0
16	95.7	95.8	95.0
18	11.7	11.2	10.9
19	24.0	22.5	22.5
20	41.3	36.8	37.3
21	65.6	78.7	73.6
22	–	–	65.2
CO_2*Me*	51.2	51.5	50.2
CO_2Me	168.9	168.0	167.5

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

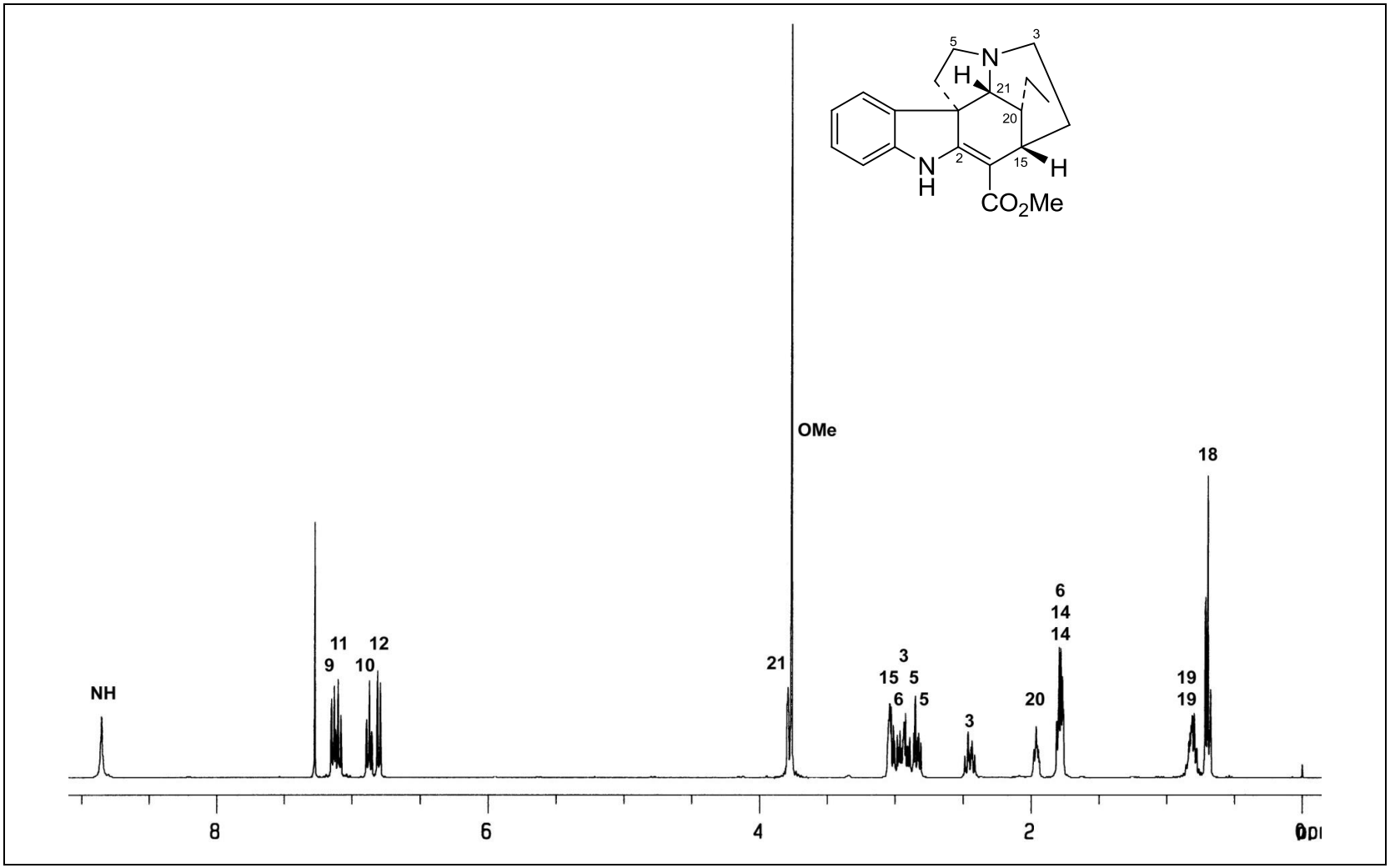


Figure 2.79: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of tubotaiwine (**57**)

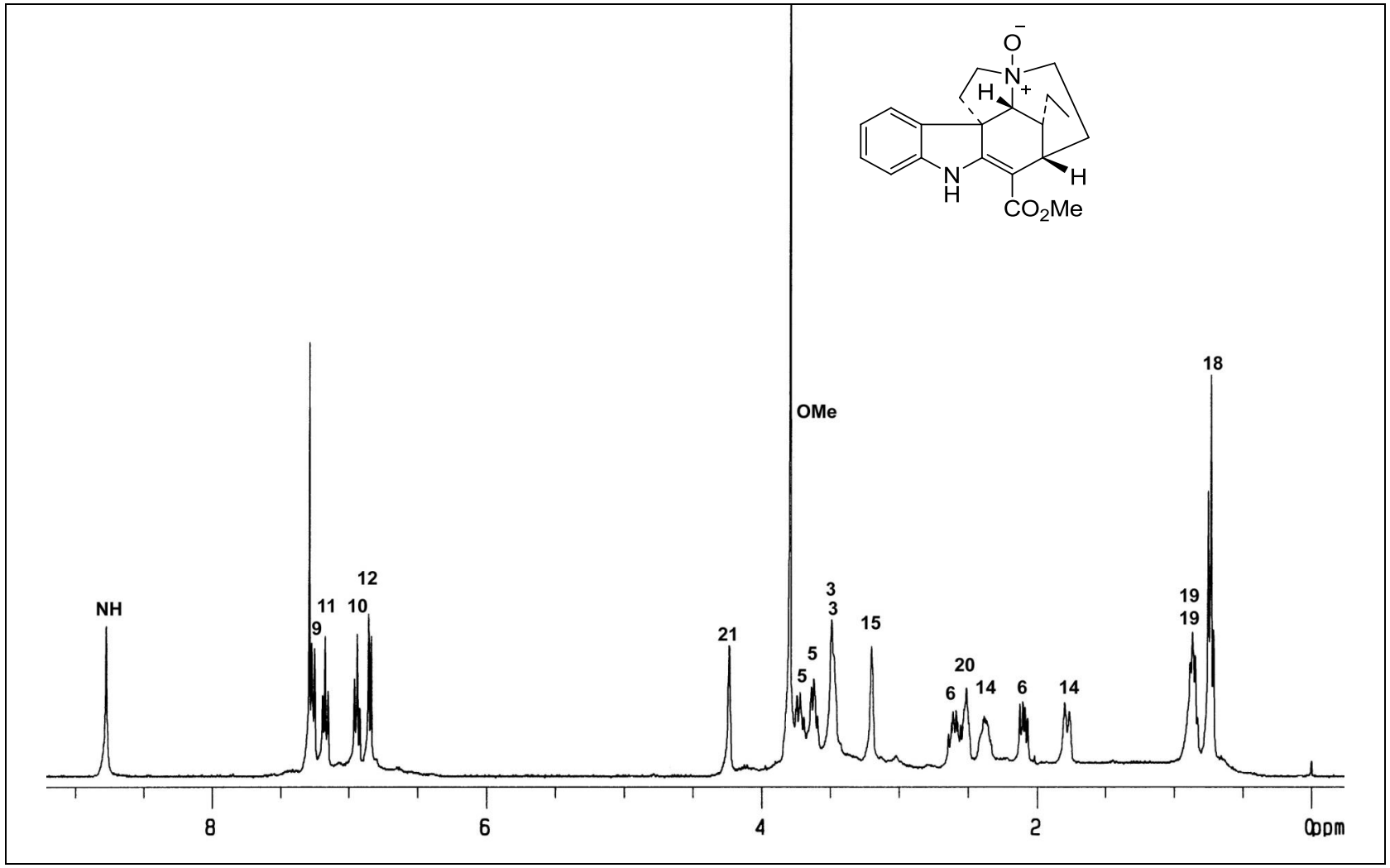


Figure 2.80: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of tubotaiwine *N*-oxide (**58**)

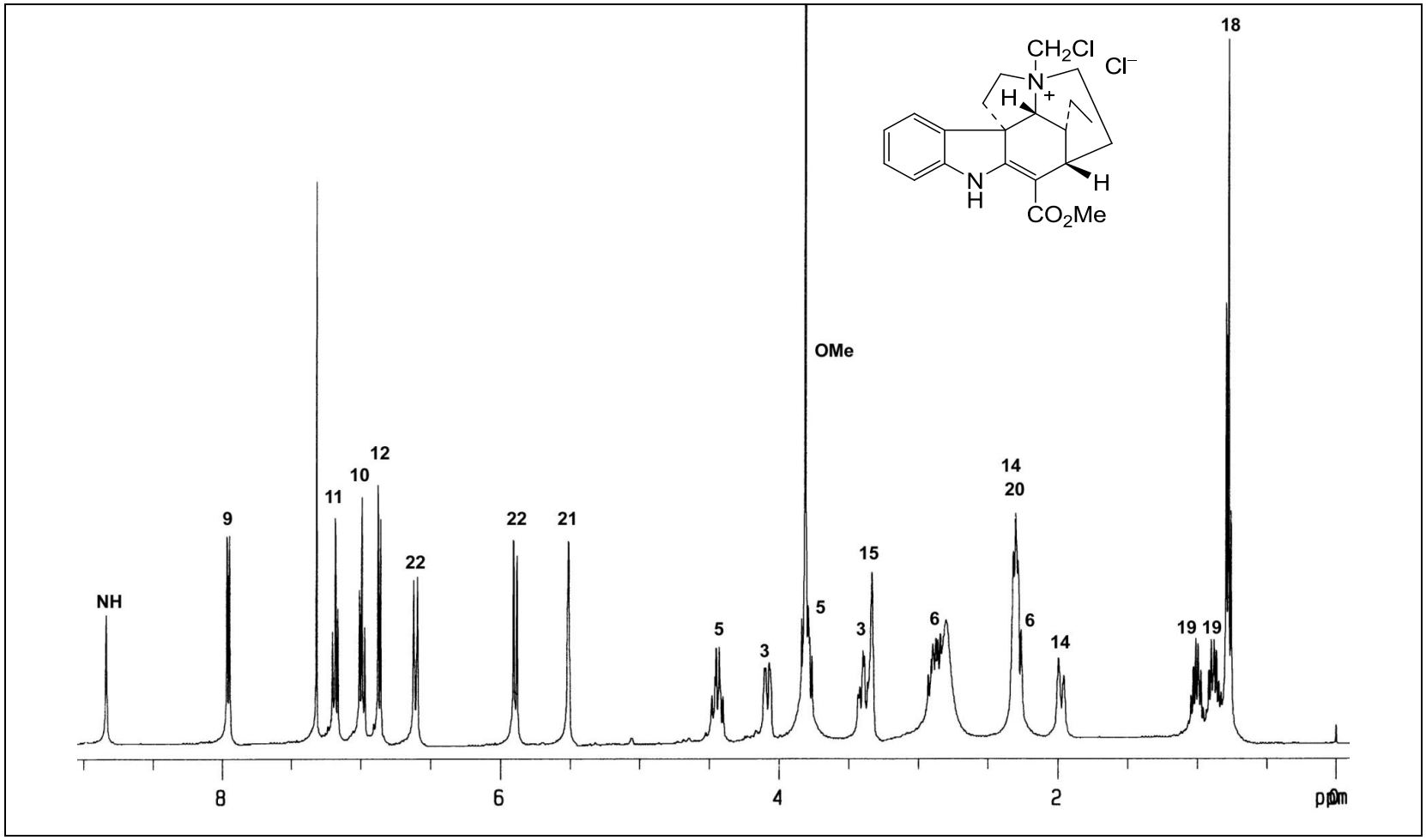


Figure 2.81: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *N*(4)-chloromethyltubotaiwine chloride (**59**)

2.1.9 Monoterpene Alkaloids and Lignans

2.1.9.1 Venoterpine (60) and Syringaresinol (61)

One known monoterpene indole alkaloid, venoterpine (**60**)[350,351] and one known lignan, syringaresinol (**61**),[352-354] were isolated in this study. The ^{1}H NMR spectra of these compounds are shown in Figures 2.82 and 2.83, while the NMR spectroscopic data are summarized in Table 2.39. Other data are given in the Experimental Section.

Table 2.39: ^{1}H and ^{13}C NMR Spectroscopic Data of and Venoterpine (**60**) and Syringaresinol (**61**)[a]

Position	**60**		Position	**61**	
	δ_H	δ_C		δ_H	δ_C
1	8.37 s	147.6	1, 5	3.10 m	54.2
3	8.35 d (5)	145.1	4, 8	3.91 m	71.6
4	7.18 d (5)	120.4		4.29 m	
5	–	150.4	2, 6	4.73 d (5)	85.9
6	2.93 dd (17, 2)	40.9	1', 1"	–	131.9
	3.12 dd (17, 5)		2', 2"	6.59 br s	102.6
7	4.58 td (5, 2)	75.2	3', 3"	–	147.1
8	3.24 qd (7, 5)	42.7	4', 4"	–	134.2
9	–	141.9	5', 5"	–	147.1
7-OH	2.32 br s	–	6', 6"	6.59 br s	102.6
8-Me	1.39 d (7)	11.9	5'-OMe, 5"-OMe	3.90 s	56.2
			4'-OH, 4"-OH	5.60 br s	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

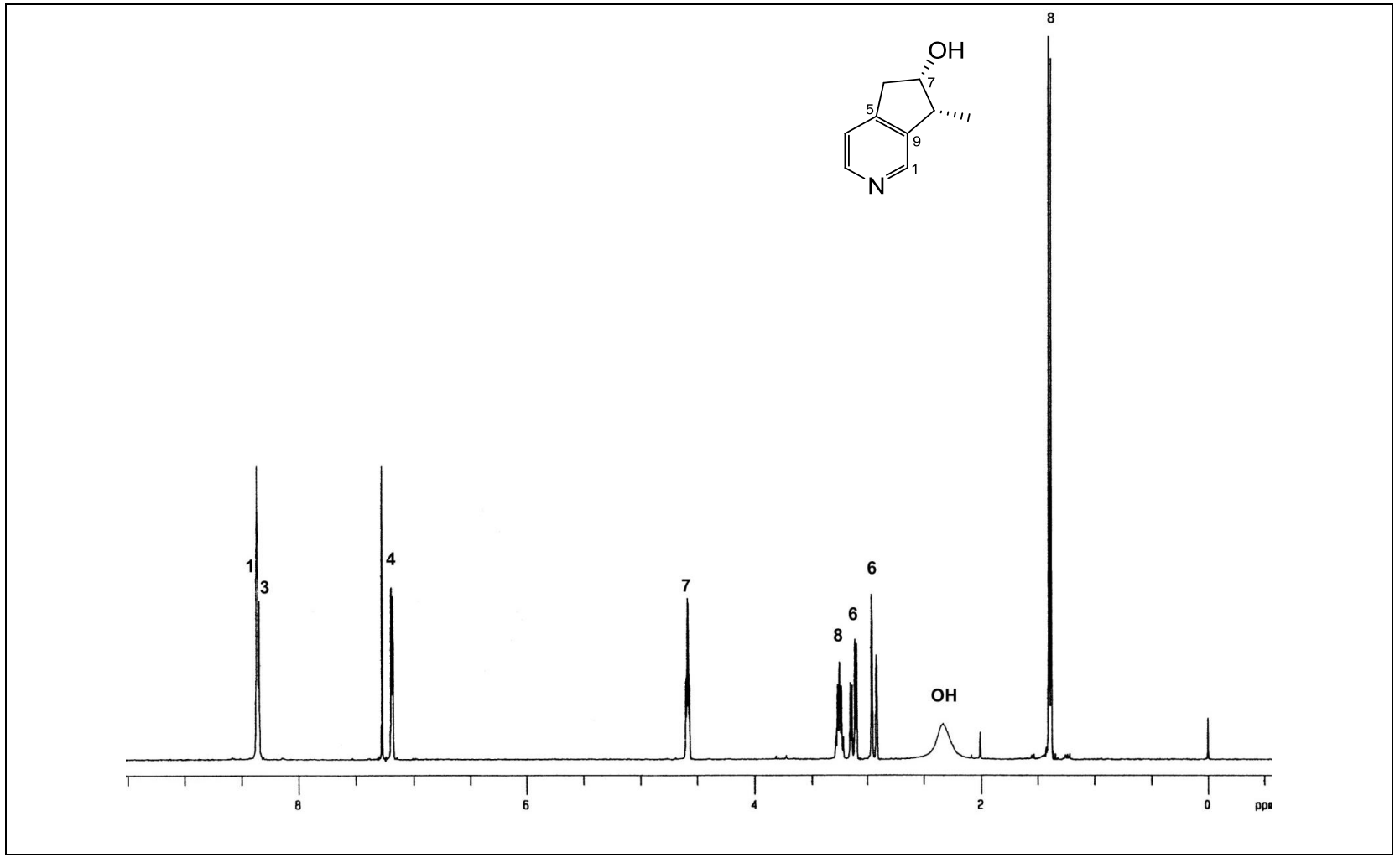


Figure 2.82: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of venoterpine (**60**)

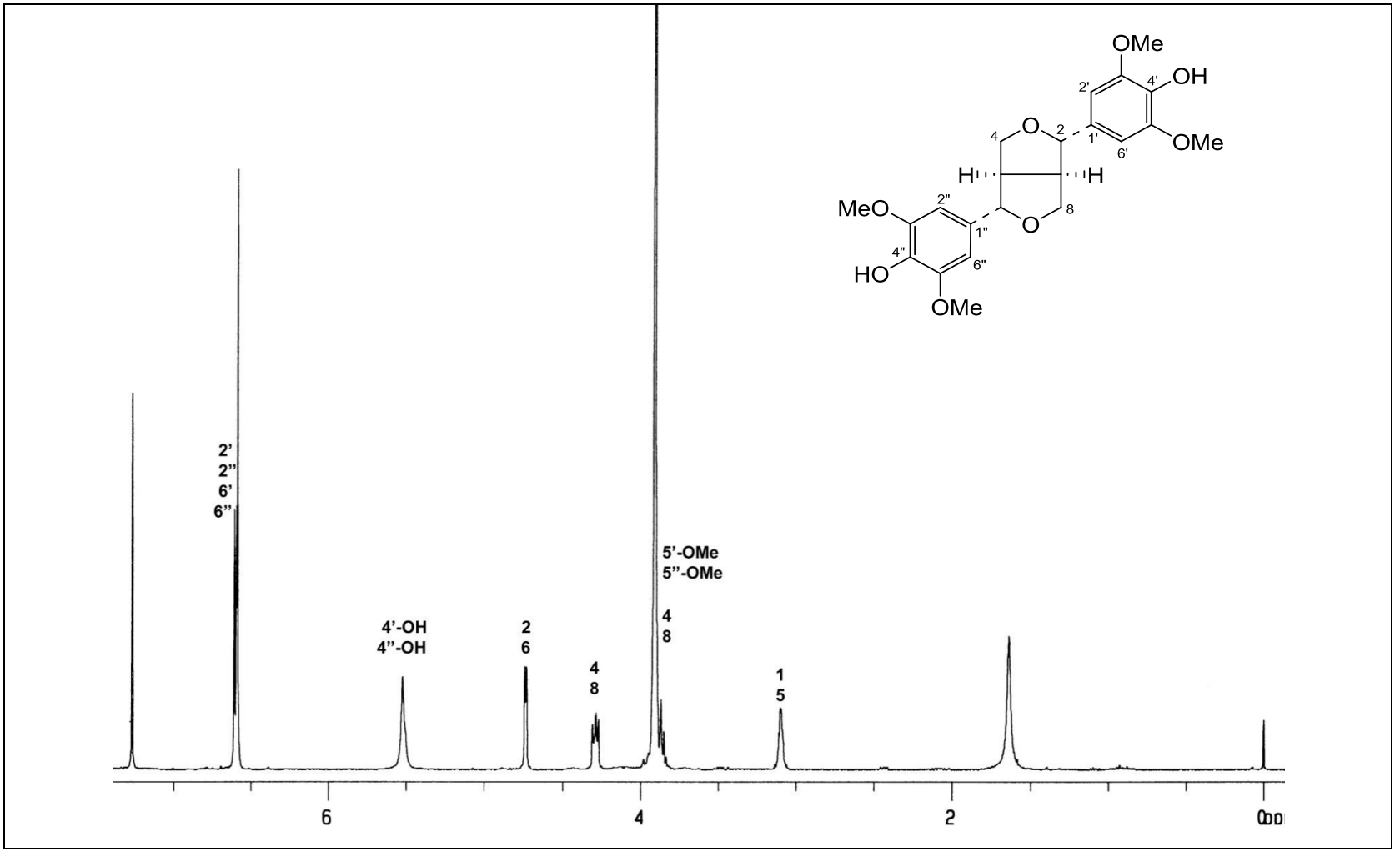
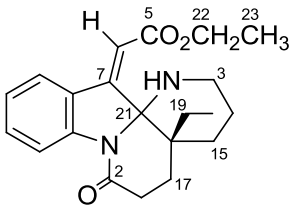


Figure 2.83: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of syringaresinol (**61**)

2.2 Alkaloids from *Kopsia pauciflora*

Investigation of the alkaloidal content of the Malayan *Kopsia pauciflora* Hook. f. has provided a total of 50 alkaloids, of which 10 are new. These new alkaloids are the *seco*-leuconoxine alkaloid, compound **62**, the eburnane derivatives, compounds **63** and **64**, the corynanthean oxindole alkaloids, compounds **69**–**71**, the corynanthean pseudoindoxyl alkaloid, tetrahydroalstonine pseudoindoxyl (**73**), the aspidofractinine derivative, 11,12-dimethoxykopsinaline (**77**), and the unusual pentacyclic indole alkaloids, andransinine (**90**) and compound **91**. Compounds **62**, **64**, **71**, **90**, and **91** showed strong ability to reverse multi-drug resistant in vincristine-resistant KB (VJ300) cells. The alkaloid composition of *K. pauciflora* is summarized in Table 2.40.



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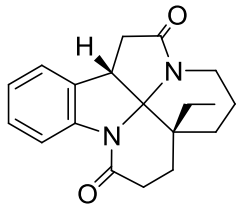

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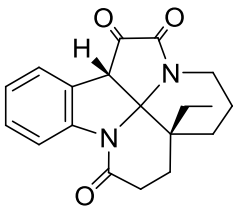

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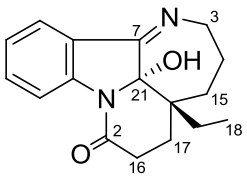

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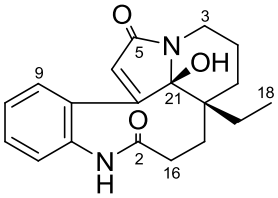

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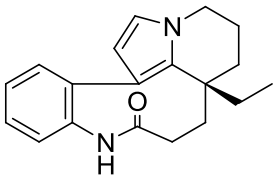

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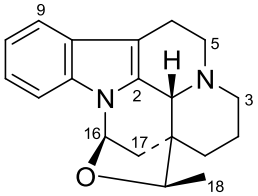

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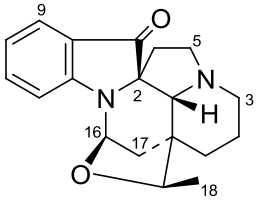

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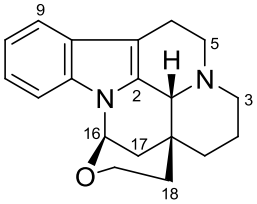

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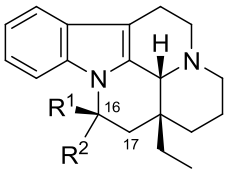
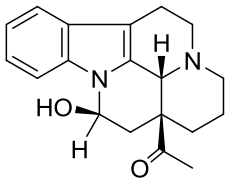


29 R^1, R^2 = O
30 R^1 = H, R^2 = nil $\Delta^{16,17}$
33 R^1 = H, R^2 = OH
34 R^1 = OH, R^2 = H



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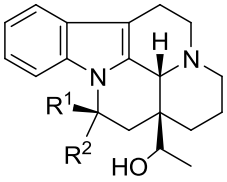
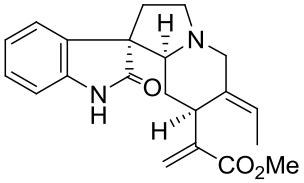


67 R^1 = H, R^2 = OH
68 R^1 = OH, R^2 = H



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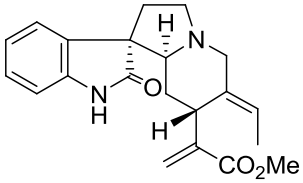

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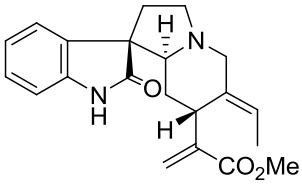

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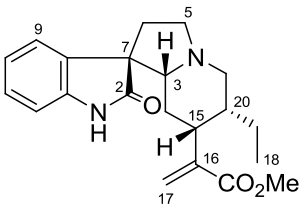

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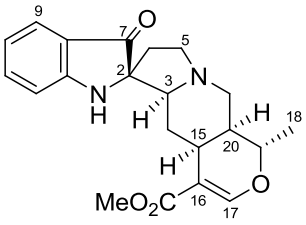

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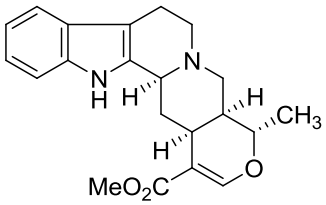

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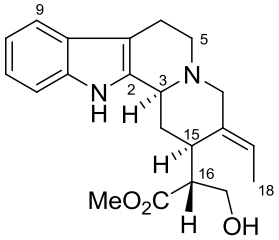

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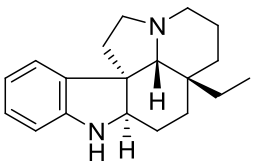

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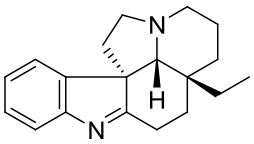

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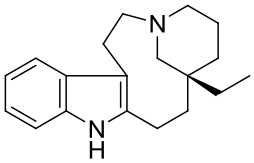

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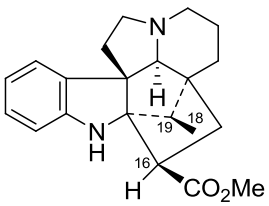

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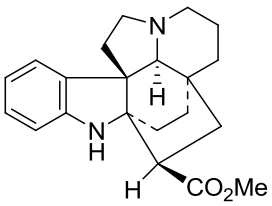

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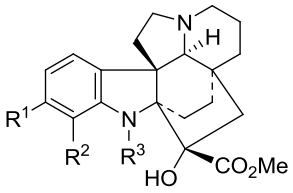
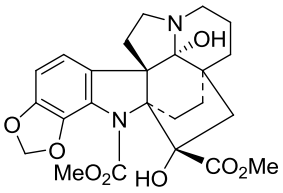
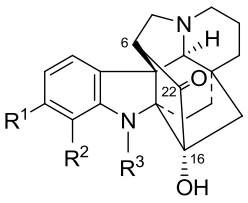


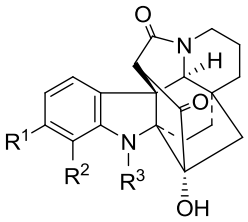
77 $R^1 = R^2 = OMe$, $R^3 = H$
80 $R^1,R^2 = OCH_2O$, $R^3 = CO_2Me$
81 $R^1,R^2 = OCH_2O$, $R^3 = H$
82 $R^1 = H$, $R^2 = OMe$, $R^3 = CO_2Me$



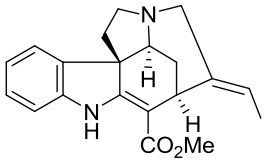
83



84 $R^1 = R^2 = R^3 = H$
85 $R^1,R^2 = OCH_2O$, $R^3 = CO_2Me$
86 $R^1 = H$, $R^2 = OMe$, $R^3 = CO_2Me$



87 $R^1,R^2 = OCH_2O$, $R^3 = CO_2Me$
88 $R^1,R^2 = OCH_2O$, $R^3 = H$



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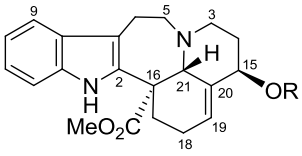
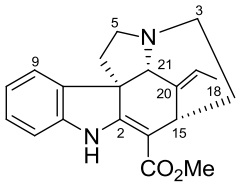


90 $R = CH_2CH_3$
91 $R = CH_3$



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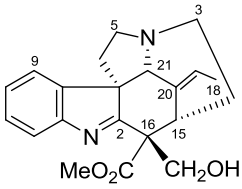

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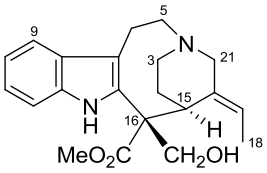
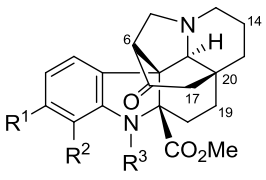
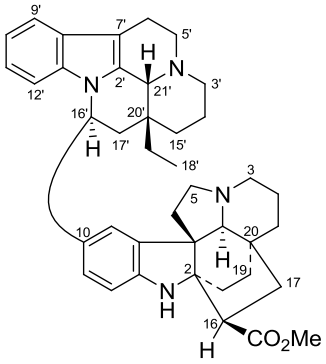


94



95 $R^1,R^2 = OCH_2O$, $R^3 = H$
96 $R^1,R^2 = OCH_2O$, $R^3 = CO_2Me$
97 $R^1 = R^2 = H$, $R^3 = CO_2Me$
98 $R^1 = R^2 = R^3 = H$
99 $R^1 = H$, $R^2 = OMe$, $R^3 = CO_2Me$



100

Table 2.40: Alkaloid Composition of *K. pauciflora*

Plant part	Alkaloid	Yield (g kg^{-1})
Stem-bark (19 kg)	Leuconoxine (**14**)	0.0027
	Rhazinilam (**25**)	0.0015
	Compound **63** [New]	0.0047
	Compound **64** [New]	0.0040
	(+)-Eburnamonine (**29**)	0.0030
	(+)-Eburnamenine (**30**)	0.0121
	(+)-Isoeburnamine (**33**)	0.0043
	(–)-Eburnamine (**34**)	0.0531
	(+)-19-Oxoeburnamine (**66**)	0.0006
	(–)-19(*R*)-Hydroxyisoeburnamine (**67**)	0.0064
	(+)-19(*R*)-Hydroxyeburnamine (**68**)	0.0018
	Tetrahydroalstonine (**43**)	0.0136
	11,12-Dimethoxykopsinaline (**77**) [New]	0.0017
	Pseudokopsinine (**78**)	0.0258
	Kopsinine (**79**)	0.1662
	Kopsamine (**80**)	0.0880
	N(1)-Decarbomethoxykopsamine (**81**)	0.1926
	Kopsilongine (**82**)	0.0028
	Paucifinine (**83**)	0.0133
	Kopsanone (**84**)	0.0024
	11,12-Methylenedioxykopsine (**85**)	0.0029
	Kopsifine (**87**)	0.0514
	N(1)-Decarbomethoxykopsifine (**88**)	0.0010
	Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (**95**)	0.0121
	Methyl 11,12-methylenedioxychanofruticosinate (**96**)	0.0036
	(–)-Norpleiomutine (**100**)	0.0036
Leaves (8.8 kg)	Compound **62** [New]	0.0088
	Leuconoxine (**14**)	0.0055
	Leuconodine F (6-oxoleuconoxine) (**15**)	0.0007
	Mersicarpine (**16**)	0.0046
	Leuconolam (**19**)	0.0010

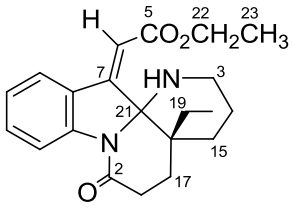
Table 2.40, continued

Plant part	Alkaloid	Yield (g kg^{-1})
	Rhazinilam (**25**)	0.0060
	Compound **63** [New]	0.0157
	Larutenine (**65**)	0.0028
	Compound **69** [New]	0.0006
	Compound **70** [New]	0.0473
	Compound **71** [New]	0.0211
	(–)-Catharinensine (**72**)	0.0048
	Tetrahydroalstonine pseudoindoxyl (**73**) [New]	0.0277
	Tetrahydroalstonine (**43**)	1.2463
	16(*R*)-19,20-*E*-Isositsirikine (**47**)	0.0003
	(+)-Aspidospermidine (**74**)	0.0105
	(+)-1,2-Dehydroaspidospermidine (**75**)	0.0592
	(–)-Quebrachamine (**76**)	0.0148
	Pseudokopsinine (**78**)	0.0016
	Kopsinine (**79**)	0.0014
	N(1)-Decarbomethoxykopsamine (**81**)	0.0224
	Paucifinine (**83**)	0.0018
	11,12-Methylenedioxykopsine (**85**)	0.0005
	12-Methoxykopsine (**86**)	0.0030
	Akuammicine (**89**)	0.0005
	Andransinine (**90**) [New]	0.0022
	Compound **91** [New]	0.0009
	Condylocarpine (**92**)	0.0031
	Precondylocarpine (**93**)	0.0047
	Stemmadenine (**94**)	0.0367
	Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (**95**)	0.0992
	Methyl 11,12-methylenedioxychanofruticosinate (**96**)	0.0915
	Methyl chanofruticosinate (**97**)	0.0791
	Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)	0.1594
	Methyl 12-methoxychanofruticosinate (**99**)	0.0648

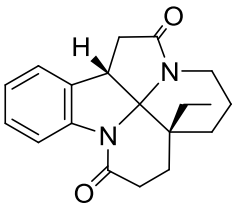
2.2.1 Leuconoxine–Leuconolam–Rhazinilam Alkaloids

2.2.1.1 Compound 62

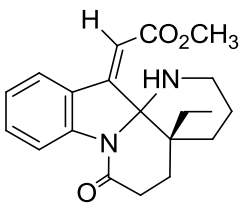
Compound **62** was obtained from the leaf extract of *K. pauciflora* as a yellowish oil with $[\alpha]_D$ +72 ($CHCl_3$, *c* 0.87). The UV spectrum of **62** showed absorption maxima at 246, 271, and 326 nm, indicating the presence of an *N*-acyl dihydroindole (*e.g.*, leuconoxine (**14**)),[128] and an α,β-unsaturated ester function (*vide infra*). The IR spectrum showed bands at 3304, 1722, and 1665 cm^{-1} due to NH, ester, and lactam functionalities, respectively. The carbon resonances observed at δ 168.7 and 169.7 in the ^{13}C NMR data (Table 2.41) confirmed the presence of the ester and lactam functionalities, respectively. The ESIMS of **62** showed an $[M + H]^+$ peak at *m*/*z* 355 and the HRESIMS measurements gave the formula $C_{21}H_{26}N_2O_3$. The ^{13}C NMR data (Table 2.41) gave a total of 21 carbon resonances (two methyl, seven methylene, five methine, and seven quaternary carbons) in agreement with the molecular formula.



62



14



17

The ^1H and ^{13}C NMR data (Table 2.41) of **62** showed a close resemblance to those of arboloscine (**17**),[157] except for the absence of the methoxy singlet at δ 3.83 in **17** which in **62**, has been replaced by a 2H multiplet at δ 4.28 and a methyl triplet at δ 1.35. The COSY and HSQC data disclosed the presence of two CH_2CH_3 fragments, one was

assigned to the usual C(19)–C(18) ethyl side chain, and the other was attributed to the C(22)–C(23) ethoxy group. The ethoxy substituent was deduced to be at C(5) from the observed three bond correlation from H(22) to C(5) in the HMBC spectrum (Figure 2.84), which revealed that the carbomethoxy function in **17** was replaced by a carboethoxy function in **62**. The geometry of the exocyclic double bond at C(6)–C(7) was deduced to be similar to that in **17**, *i.e.*, *Z*, from the observed NOE (Figure 2.84) between the aromatic H(9) and the vinylic H(6). In view of the presence of the ethoxy group and the use of ethanol during extraction of alkaloids, it is likely that this compound is an artifact of the isolation process.

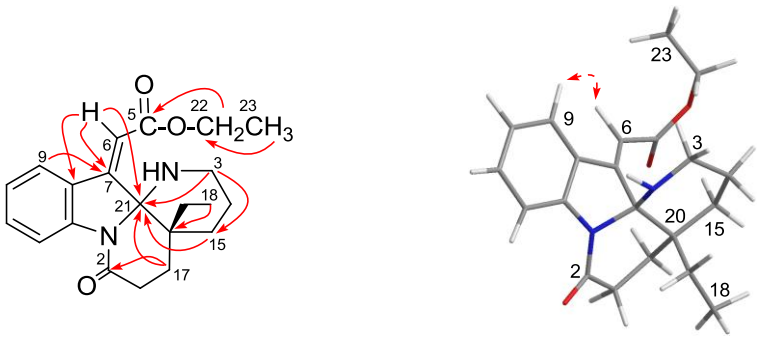
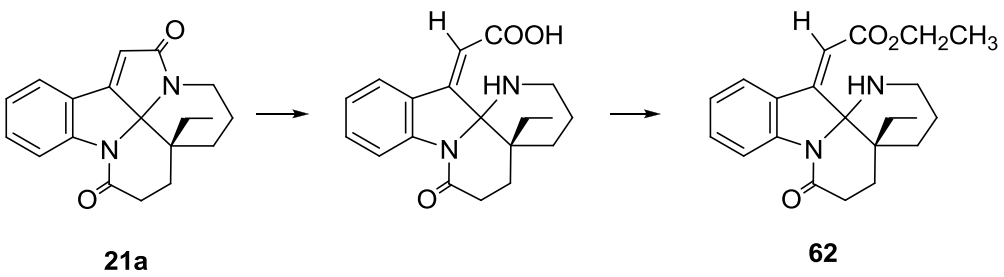


Figure 2.84: Selected HMBCs and NOEs of **62** (= HMBC; = NOE)

Compound **62** can be envisaged to have arisen from 6,7-dehydroleuconoxine (**21a**), following hydrolytic cleavage and esterification (Scheme 2.9).



21a **62**

Scheme 2.9: A possible origin of **62**[157]

Table 2.41: ^{1}H and ^{13}C NMR Spectroscopic Data of Compound **62**[a]

Position	δ_H	δ_C	HMBC		DNOE/NOESY
			^{2}J	^{3}J	
2	–	169.7			
3	2.79 m	40.4	14	15, 21	
	3.22 td (12, 3)				
5	–	168.7			
6	6.51 s	110.1	7	8, 21	9
7	–	140.1			
8	–	127.3			
9	7.43 d (8)	120.5		11, 13	6, 10
10	7.09 t (8)	124.1		8, 12	9, 11
11	7.32 t (8)	130.9		9, 13	10, 12
12	8.35 d (8)	118.5		10	11
13	–	142.5			
14	1.48 m	20.2			
	1.84 m				
15	1.64 m	30.4		21	
	1.70 m				
16	2.50 dd (17, 10)	29.9	2		
	2.74 m				
17	1.56 m	25.2	16	2, 15, 21	
	2.70 m				
18	0.82 t (7.3)	7.1	19	20	19
19	1.48 m	26.3		15, 17, 21	18
	1.74 m				
20	–	36.9			
21	–	88.1			
22	4.28 m	61.7	23	5	23
	4.28 m				
23	1.35 t (7.3)	14.2	22		22

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY/DNOE.

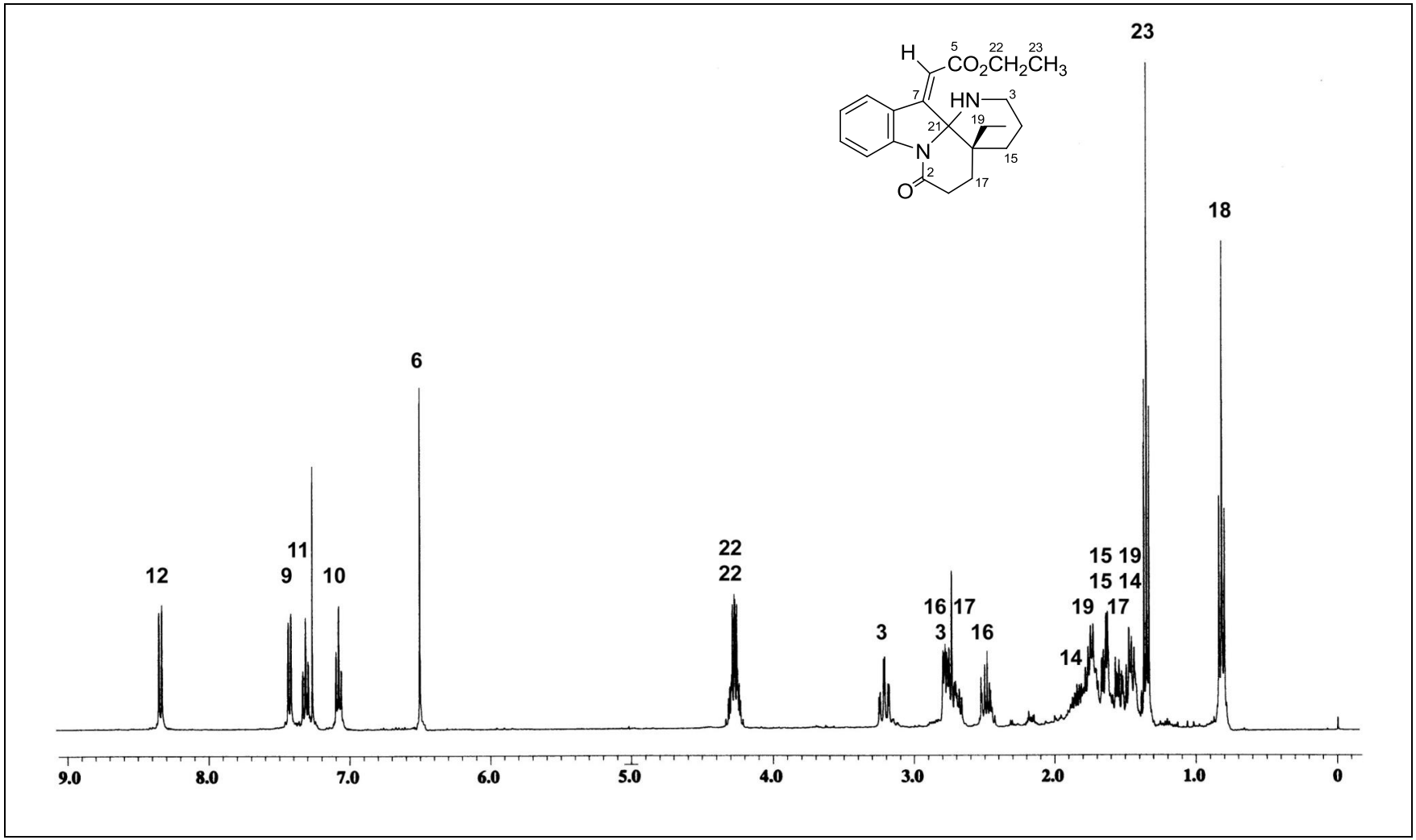


Figure 2.85: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of compound **62**

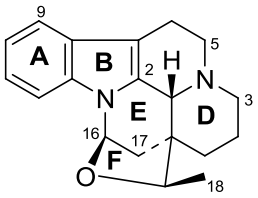
2.2.1.2 Leuconoxine (14), Leuconodine F (15), Mersicarpine (16), Leuconolam (19), and Rhazinilam (25)

Other known leuconoxine–leuconolam–rhazinilam alkaloids obtained from *K. pauciflora* include leuconoxine (**14**),[128] leuconodine F (6-oxoleuconoxine) (**15**),[208] mersicarpine (**16**),[159] leuconolam (**19**),[124,126] and rhazinilam (**25**).[124,126] These compounds were also obtained from *L. griffithii*. Their NMR spectroscopic data are presented in the previous section (section 2.1.3.9). Other data are given in the Experimental Section.

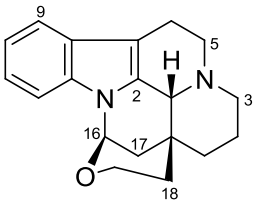
2.2.2 Eburnane Alkaloids

2.2.2.1 Compound 63

Compound **63** was obtained as a light yellowish oil, with $[\alpha]_D$ −5 ($CHCl_3$, *c* 0.10). The UV spectrum of **63** (228 and 276 nm) was typical of an indole chromophore. The IR spectrum showed the presence of Wenkert-Bohlmann bands at 2852, 2796, and 2739 cm^{-1}, indicating a *trans*-quinolizidine skeleton.[355,356] The ESIMS of **63** showed an $[M + H]^+$ peak at *m*/*z* 295, while the HRESIMS measurements established the molecular formula as $C_{19}H_{22}N_2O$ (DBE 10).



63



65

The NMR data of **63** (Table 2.42) were generally similar to those of larutenine (**65**),[214,215] with the presence of signals due to an unsubstituted indole moiety (δ 7.42, br d, *J* = 8 Hz, H(9); 7.05, td, *J* = 8, 1 Hz, H(10); 7.15, td, *J* = 8, 1 Hz, H(11); 7.38, br d, *J* = 8 Hz, H(12)), an isolated aminomethine due to H(21) at δ 3.23 (axial bridgehead hydrogen within a *trans*-quinolizidine skeleton), and the characteristic H(16) signal at δ 5.92 (d, *J* = 4 Hz). However, the main differences were the changes involving ring F. Compared with **65**, a methyl doublet and an oxymethine were seen at δ 1.33 (*J* = 6.3 Hz) and 3.95 (q, *J* = 6.3 Hz), respectively, in the ^{1}H NMR spectrum of **63** (Figure 2.88). Analysis of the COSY and HSQC data revealed an -OCHCH$_3$ fragment corresponding to OC(19)–C(18) unit, in place of the -OCH$_2$CH$_2$ fragment seen in **65**. This observation suggests that the 6-membered (tetrahydropyran) ring F in **65** has been reduced to a 5-membered (tetrahydrofuran) ring with a methyl substituent at C(19) in **63**.

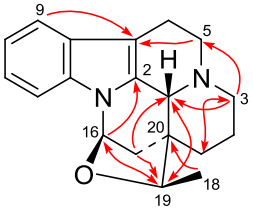


Figure 2.86: Selected HMBCs of **63**

This was supported by the observed three-bond correlations from H(18) to C(20), and from H(19) to C(16) and C(21) in the HMBC spectrum. The structure proposed is in agreement with the HMBC data (Figure 2.86). The configurations of C(20) and C(21)

are assumed to be similar to those in (+)-eburnamonine (**29**), (+)-eburnamenine (**30**), (+)-isoeburnamine (**33**), and (–)-eburnamine (**34**)[214] found in this plant, *i.e.*, 20*R*, 21*R* (or 20β, 21β) assuming that they are biogenetically related). It therefore follows the stereochemistry of the C(16) ether oxygen has to be β to permit the formation of the sixth ring (ring F) in **63**.

2.2.2.2 Compound 64

Compound **64** was isolated as a light yellowish oil and subsequently light yellowish crystals from CH_2Cl_2–MeOH, mp 190–192 ^oC, $[\alpha]_D$ +381 ($CHCl_3$, *c* 0.16). The UV spectrum showed absorption maxima at 210, 234, 257, 308, and 376 nm typical of an indole and pseudoindoxyl chromophores.[357] The IR spectrum also showed similar Wenkert-Bohlmann bands at 2855, 2799, and 2742 cm^{-1}, indicating the presence of a *trans*-quinolizidine skeleton,[355,356] in addition to a ketone function at 1610 cm^{-1}. The ESIMS of **64** showed an $[M + H]^+$ peak at *m*/*z* 311, while the HRESIMS measurements established the molecular formula as $C_{19}H_{22}N_2O_2$ (DBE 10, 16 mass units higher than compound **63**). The ^{13}C NMR data (Table 2.42) showed a total of 19 carbon resonances, comprising one methyl, six methylene, seven methine, and five quaternary carbon atoms, in agreement with the molecular formula.

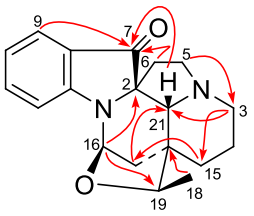


Figure 2.87: Selected HMBCs of **64**

The NMR data of **64** were in all other respect similar to those of compound **63**, except for the carbon resonances associated with C(2) and C(7). In **64**, the carbon chemical shifts for C(2) and C(7) were seen at δ 73.1 and 207.2, respectively, consistent with the presence of a ketone function (pseudoindoxyl function)[114,116,358] at C(7). This observation was further supported by the HMBC data (Figure 2.87), which showed three-bond correlations from H(6), H(9), and H(21) to C(7). The rigid architecture of the molecule restricts the configuration at C(2) to *R*. This is consistent with the observed upfield shifts of the H(18) and H(21) signals in **64** when compared to those in **63**, due probably to the anisotropic effect caused by the C(7) ketone carbonyl function.

Table 2.42: ^{1}H and ^{13}C NMR Spectroscopic Data of Compounds **63** and **64**[a]

Position	**63**		**64**	
	δ_H	δ_C	δ_H	δ_C
2	–	135.1	–	73.1
3	2.18 td (11, 3)	53.5	2.60 ddd (11.3, 8.6, 5.9)	52.9
	2.95 br d (11)		3.05 m	
5	2.74 td (11, 6.3)	54.6	2.27 td (10.6, 4.2)	51.0
	3.24 dd (12, 8)		3.08 m	
6	2.86 ddd (16, 6.3, 1.4)	22.0	1.96 m	40.8
	3.03 dddd (16, 11, 8, 2)		1.98 m	
7	–	109.4	–	207.2
8	–	128.7	–	126.4
9	7.42 br d (8)	118.7	7.67 br d (7.7)	124.6
10	7.05 td (8, 1)	119.9	7.05 td (7.7, 1.4)	122.4
11	7.15 td (8, 1)	121.6	7.56 td (7.7, 1.4)	136.6
12	7.38 br d (8)	109.7	7.20 br d (7.7)	116.9
13	–	136.5	–	162.3
14	1.75 m	23.9	1.70 m	23.7
	1.75 m		1.70 m	
15	1.58 m	30.3	1.40 m	29.7
	1.67 m		1.49 br d (11)	
16	5.92 d (4)	83.4	5.56 d (5.5)	89.2
17α	1.80 m	41.6	1.70 m	37.5
17β	1.87 d (11)		2.94 d (11)	
18	1.33 d (6.3)	16.0	0.86 d (6.8)	14.5
19	3.95 q (6.3)	83.2	3.56 q (6.8)	81.7
20	–	41.8	–	43.8
21	3.23 s	60.9	2.65 s	66.3

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

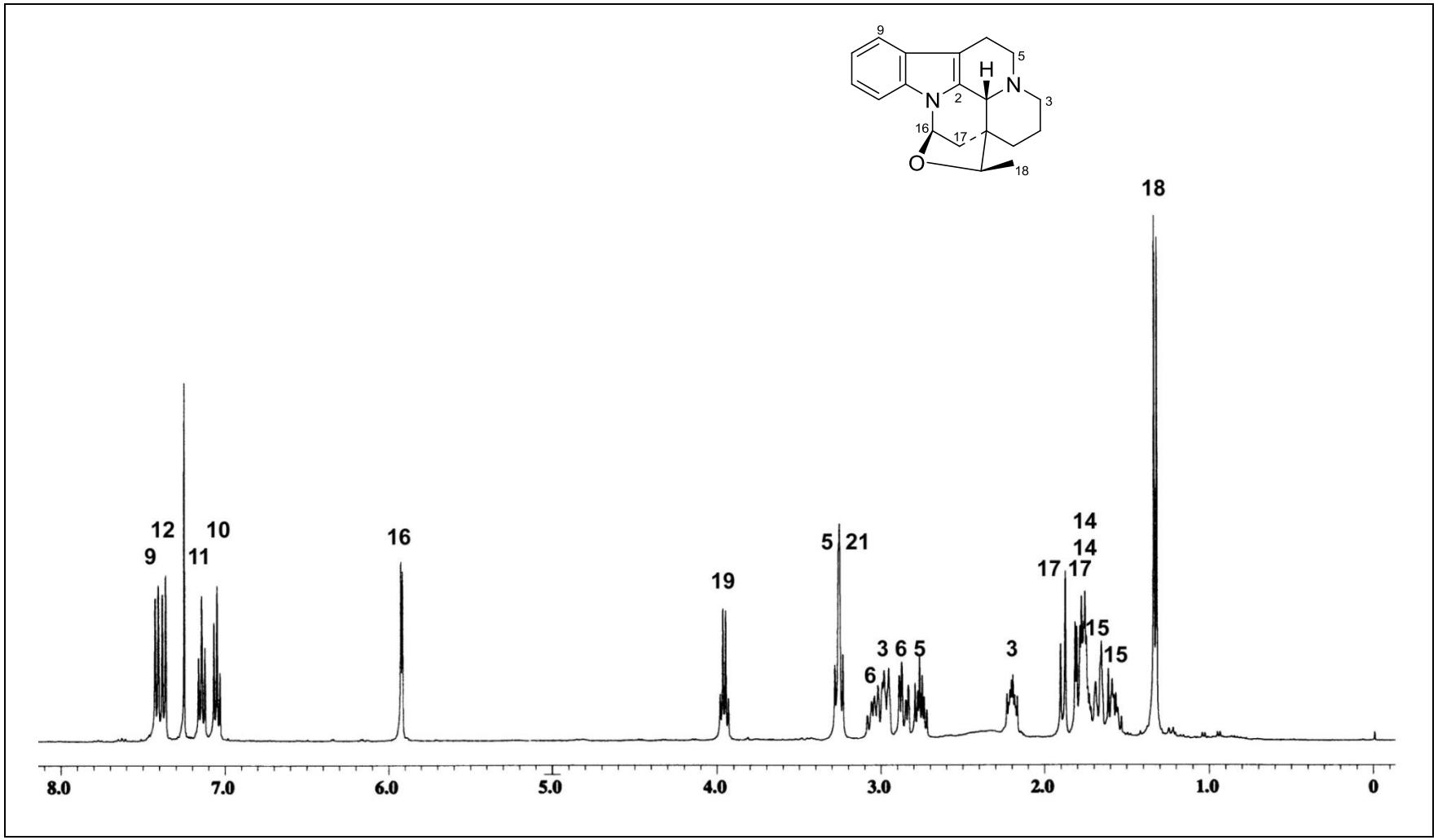


Figure 2.88: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of compound **63**

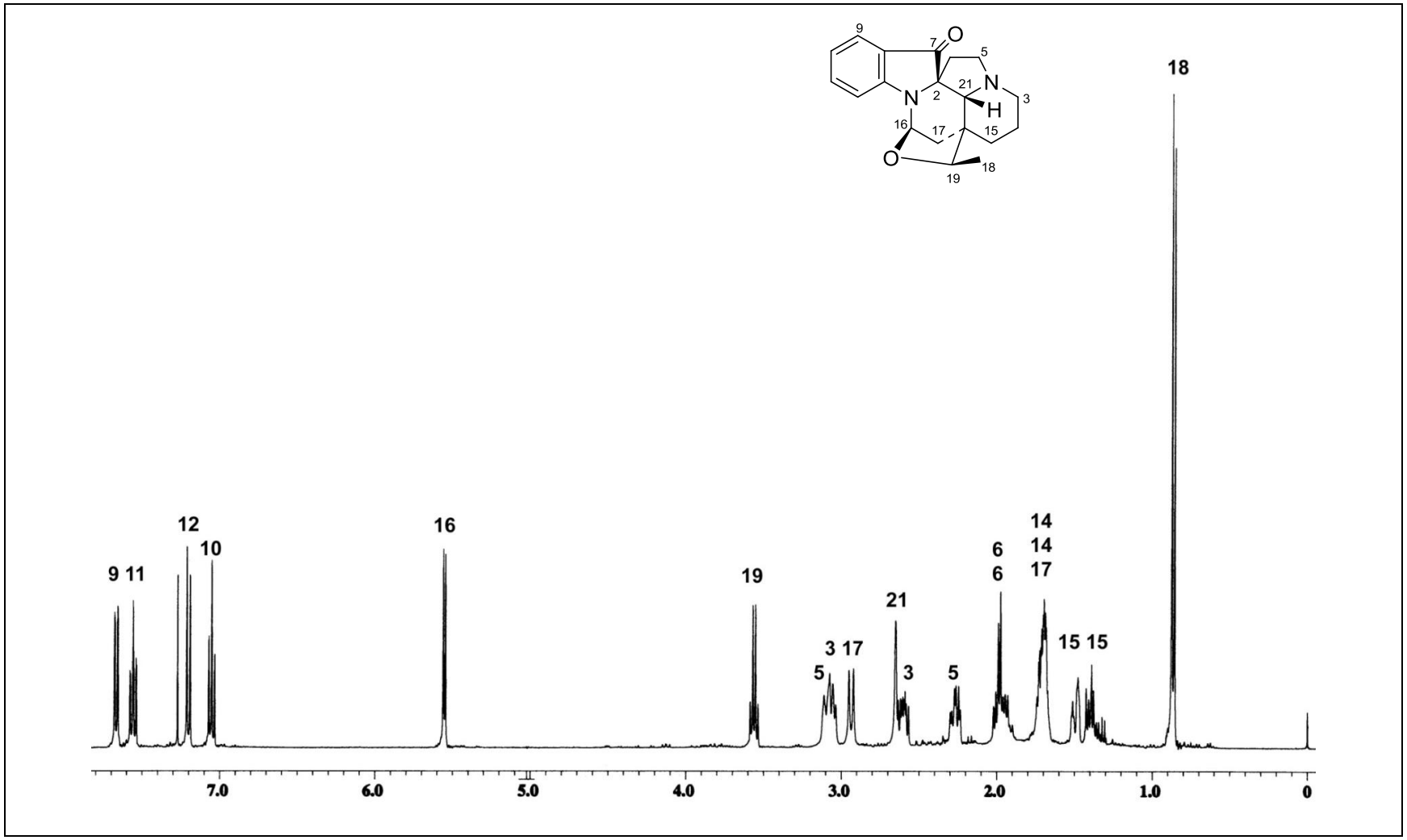


Figure 2.89: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of compound **64**

2.2.2.3 Larutenine (65), (+)-19-Oxoeburnamine (66), (–)-19(*R*)-Hydroxyisoeburnamine (67), (+)-19(*R*)-Hydroxyeburnamine (68), (+)-Eburnamonine (29), (+)-Eburnamenine (30), (+)-Isoeburnamine (33), and (–)-Eburnamine (34)

Eight known alkaloids belonging to this group, *viz.*, larutenine (**65**),[214,215] (+)-19-oxoeburnamine (**66**),[224] (–)-19(*R*)-hydroxyisoeburnamine (**67**),[188,189] (+)-19(*R*)-hydroxyeburnamine (**68**),[188,189] (+)-eburnamonine (**29**),[214] (+)-eburnamenine (**30**),[211] (+)-isoeburnamine (**33**),[214,215] and (–)-eburnamine (**34**)[214] were also isolated. The ^{1}H NMR spectra of **65**–**68** are shown in Figures 2.90–2.93, while the NMR spectroscopic data are summarized in Tables 2.43–2.45. Compounds **29, 30, 33, 34** were also obtained from *L. griffithii.* Their NMR spectroscopic data are presented in the previous section (section 2.1.4.2). Other data are given in the Experimental Section.

Table 2.43: ^{1}H and ^{13}C NMR Spectroscopic Data of Larutenine (**65**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	136.5	14	1.70 m	20.0
3	2.25 m	51.8		1.70 m	
	3.00 m		15	1.42 m	35.5
5	2.70 td (11, 7)	54.2		1.70 m	
	3.24 dd (11, 7)		16	5.83 t (2)	77.5
6	2.84 br ddd (15, 7, 1.5)	21.1	17	1.70 m	38.0
	3.00 m			1.70 m	
7	–	107.7	18	3.80 dd (13, 6)	58.5
8	–	128.5		3.95 td (13, 3)	
9	7.46 d (7)	118.3	19	1.54 br d (13)	40.6
10	7.11 t (7)	120.1		1.82 td (13, 6)	
11	7.18 t (7)	121.5	20	–	28.8
12	7.41 d (7)	109.5	21	3.17 s	63.3
13	–	137.7			

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

Table 2.44: ^{1}H NMR Spectroscopic Data of (+)-19-Oxoeburnamine (**66**), (–)-19(*R*)-Hydroxyisoeburnamine (**67**), and (+)-19(*R*)-Hydroxyeburnamine (**68**)[a]

H	**66**	**67**	**68**
3	2.36 m	2.66 m	2.42 td (13, 4)
	2.49 m	2.66 m	2.57 m
5	3.22 m	3.28 ddd (14, 6.5, 1.5)	3.28 ddd (13, 6.5, 1.5)
	3.22 m	3.33 ddd (13, 11.5, 5)	3.33 ddd (13, 11.5, 5)
6	2.49 m	2.59 ddt (16, 5, 1.5)	2.57 m
	2.95 m	3.00 dddd (16, 11.5, 6.5, 2.5)	2.97 dddd (16, 11.5, 6.5, 2.5)
9	7.49 dd (6, 2)	7.50 br d (7)	7.49 dd (7, 1.5)
10	7.16 m	7.15 td (7, 1.5)	7.17 td (7, 1.5)
11	7.19 m	7.20 td (7, 1.5)	7.21 td (7, 1.5)
12	7.71 dd (6, 2)	7.40 br d (7)	7.72 dd (7, 1.5)
14	1.43 m	1.38 br d (14)	1.32 br d (13)
	1.43 m	2.24 m	2.19 qt (13, 4)
15	0.93 br td (13, 5)	1.75 td (14, 4)	0.89 tdd (13, 4, 1)
	2.04 br d (13)	1.82 td (14, 4.5)	1.74 br d (13)
16	5.62 dd (9, 5)	6.02 dd (5, 1)	5.59 dd (10, 5)
17	1.70 dd (14, 9)	1.85 dd (15, 5)	1.58 br d (15)
	2.30 m	2.02 dd (15, 1)	2.25 dd (14, 5)
18	2.36 s	1.25 d (6.5)	1.24 d (6.5)
19	–	3.91 qd (6.5, 1)	3.98 qd (6.5, 1)
21	4.67 s	4.18 br s	4.22 br s

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

Table 2.45: ^{13}C NMR Spectroscopic Data of (+)-19-Oxoeburnamine (**66**), (–)-19(*R*)-Hydroxyisoeburnamine (**67**), and (+)-19(*R*)-Hydroxyeburnamine (**68**)[a]

C	**66**	**67**	**68**
2	131.5	129.6	130.9
3	44.0	44.4	43.7
5	50.6	51.2	50.5
6	16.8	17.0	16.7
7	106.6	105.5	105.6
8	128.7	129.1	128.6
9	118.2	118.9	118.2
10	120.4	120.6	120.4
11	121.6	121.7	121.6
12	112.0	110.2	112.1
13	136.7	135.1	136.6
14	22.6	21.9	21.2
15	24.9	23.9	22.4
16	76.3	74.5	76.5
17	42.0	39.6	43.0
18	25.6	17.8	17.6
19	210.3	79.5	78.3
20	51.7	37.4	39.5
21	54.8	60.1	59.5

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

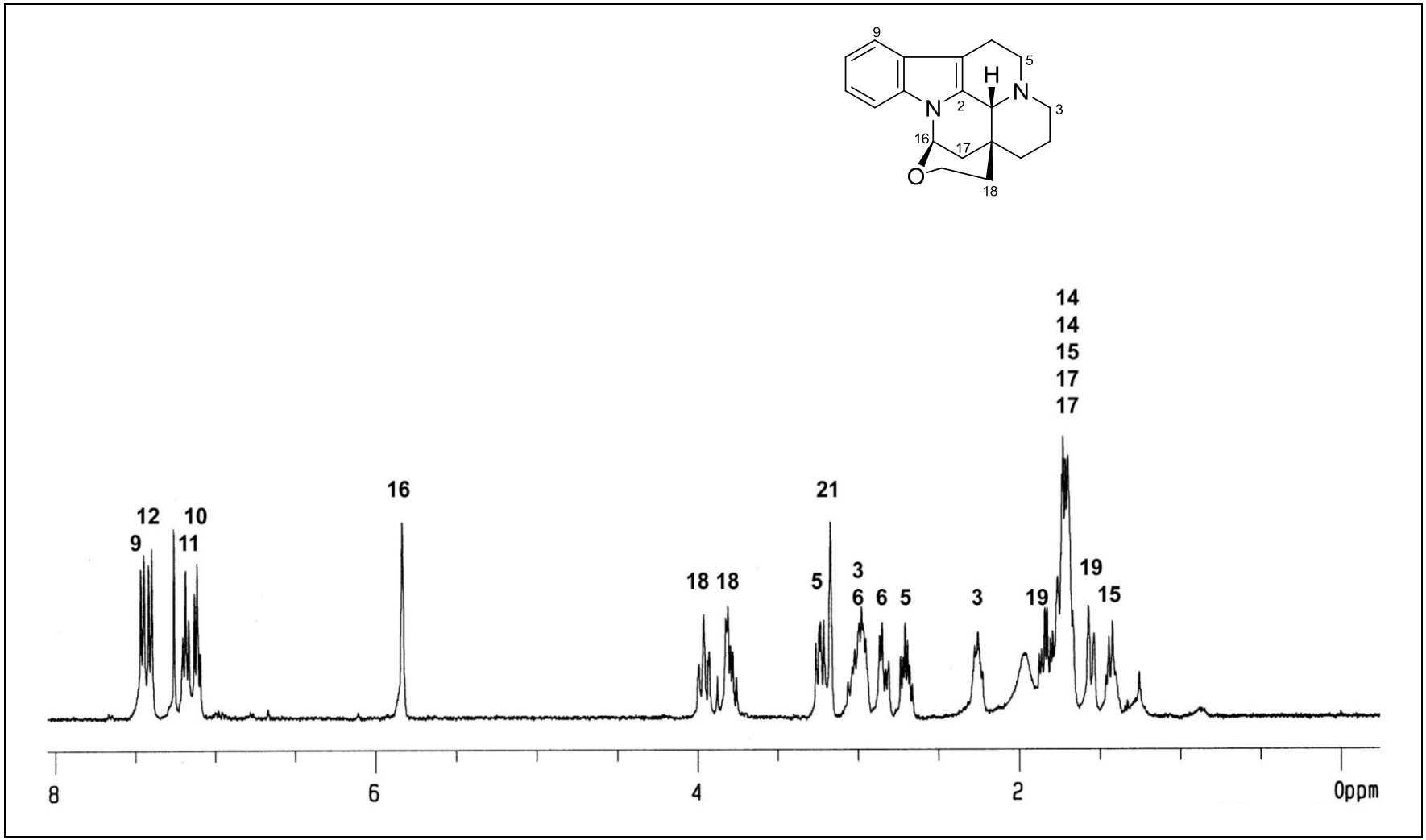


Figure 2.90: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of larutenine (**65)**

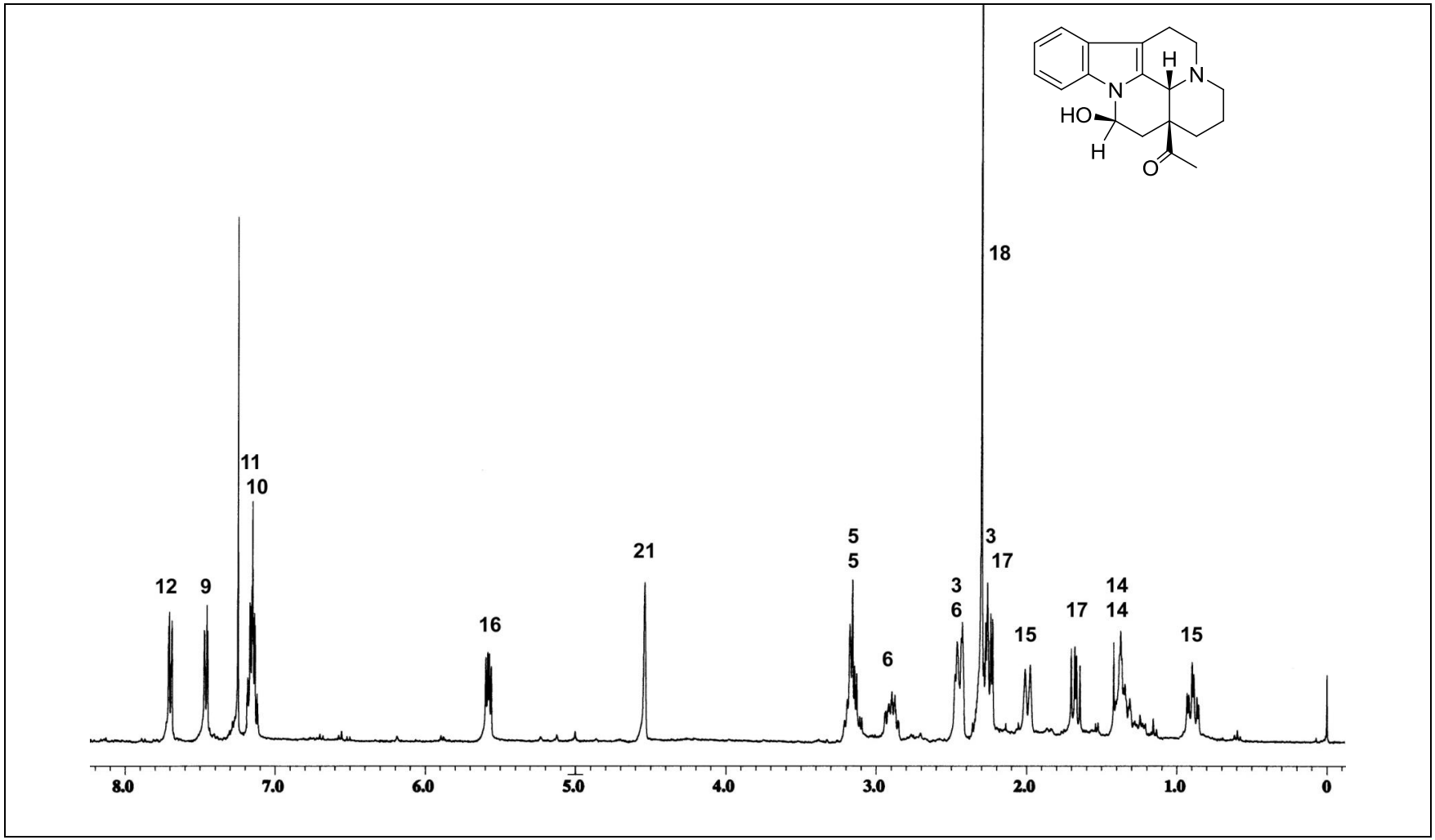


Figure 2.91: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (+)-19-oxoeburnamine (**66**)

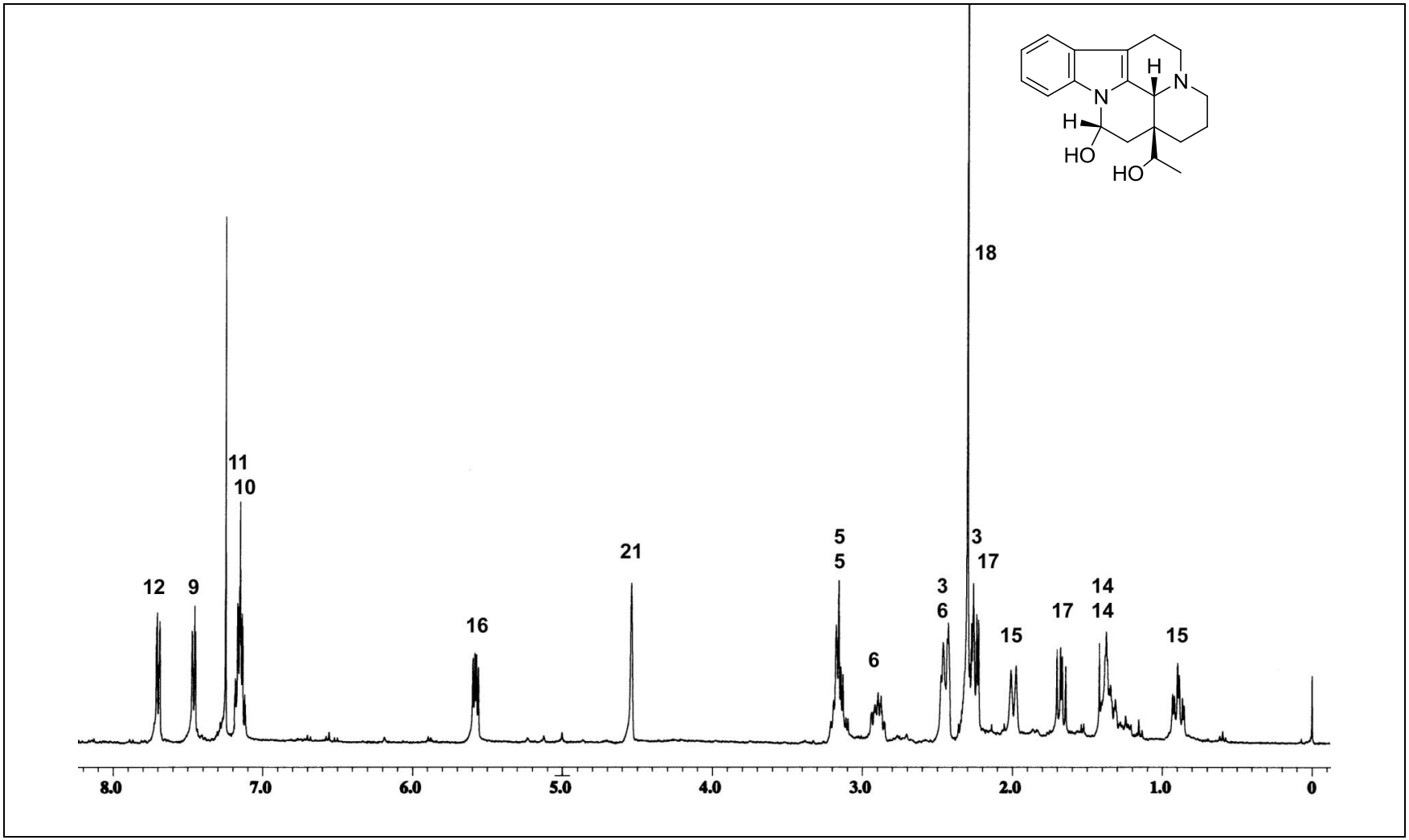


Figure 2.92: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (–)-19(*R*)-hydroxyisoeburnamine (**67**)

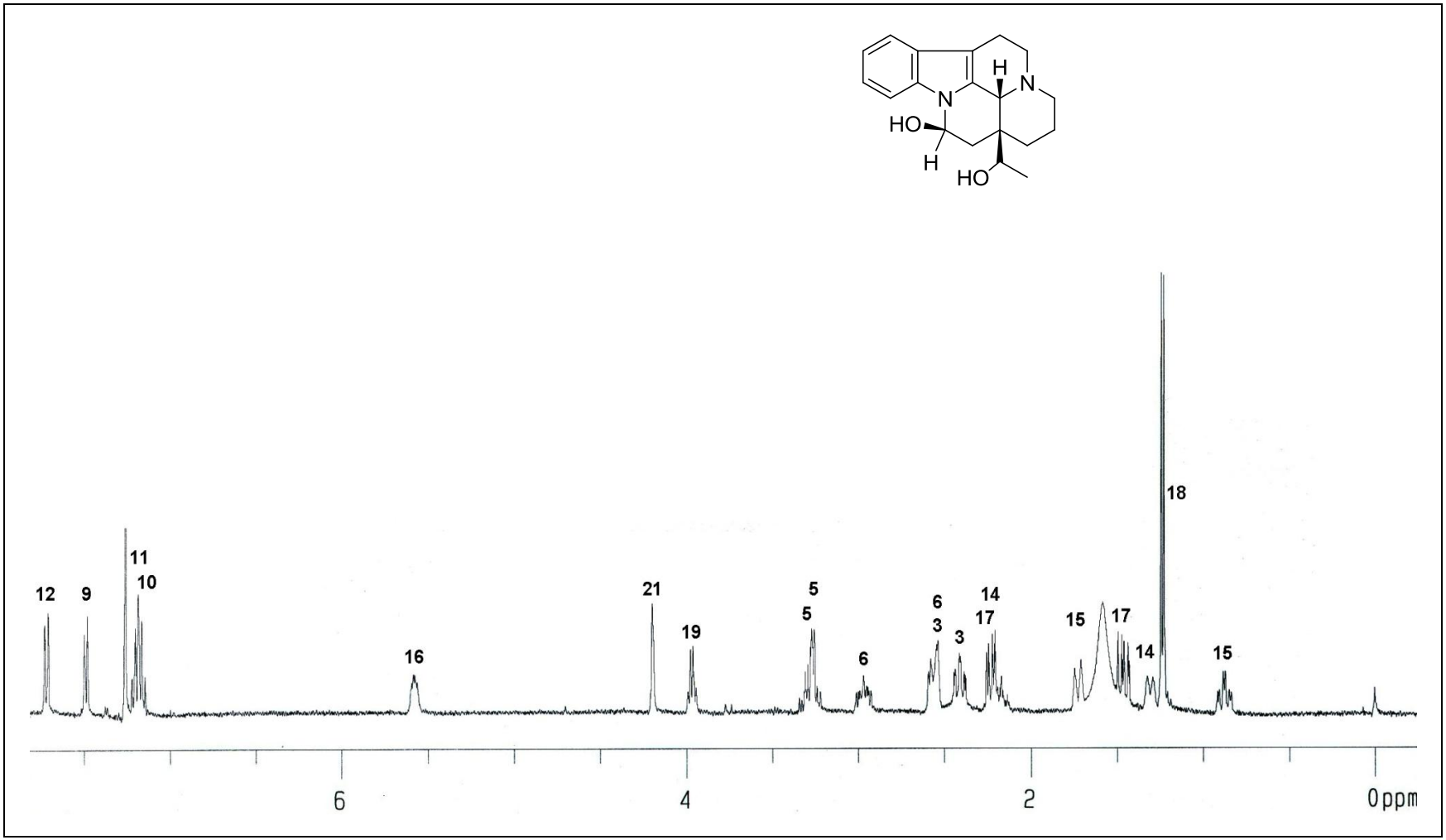
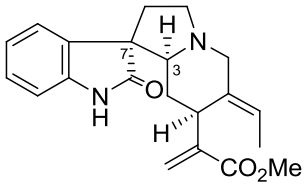


Figure 2.93: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (+)-19(*R*)-hydroxyeburnamine (**68**)

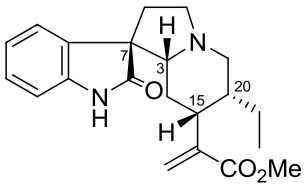
2.2.3 Corynanthe Alkaloids

2.2.3.1 Compound 69

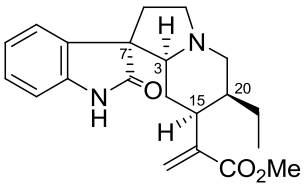
Compound **69** was isolated as a light yellowish oil from the leaf extract of *K. pauciflora*, $[\alpha]_D$ −13 ($CHCl_3$, *c* 0.02). The UV spectrum showed absorption maxima at 208, 253, and 284 nm, indicative of an oxindole chromophore.[359-361] The IR spectrum indicated the presence of NH (3434 cm^{-1}), Wenkert-Bohlmann bands (2874 and 2796 cm^{-1}), ester (1723 cm^{-1}), and lactam carbonyl (1716 cm^{-1}) functions. The ESIMS of **69** showed a quasi molecular ion at *m/z* 353, and HRESIMS measurements established the molecular formula as $C_{21}H_{24}N_2O_3$ (DBE 11).



69



(–)-**72**
3*R*, 7*R*, 15*R*, 20*R*



(+)-**72**
3*S*, 7*S*, 15*S*, 20*S*

catharinensine (**72**) belongs to the 3*R*, 7*R* or 3*S*, 7*S* oxindole series

The ^1H and ^{13}C NMR data of **69** (Tables 2.46 and 2.47, respectively) were generally similar to those of catharinensine (**72**),[359] indicating the presence of an unsubstituted indole moiety, an indolic NH, two olefinic singlets, and a methoxy singlet. Notable differences were the absence of the signals due to the ethyl side chain in the ^1H NMR spectrum (Figure 2.97) of **69**, and the presence instead of a quartet and a methyl doublet at δ 5.45 and 1.43, respectively, suggesting that the ethyl group in **72** has been replaced by an ethylidene group in **69**.

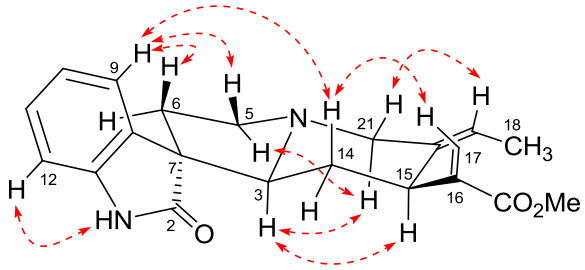


Figure 2.94: Selected NOEs of **69**

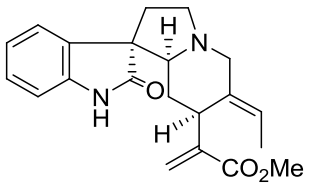
The ^{13}C NMR data of **69** are consistent with the presence of an ethylidene side chain at C(20), from the carbon resonances observed at δ 135.2 and 121.6, corresponding to the olefinic quaternary and methine carbons, respectively. The COSY and HSQC data of **69** also revealed the presence of the $CHCH_3$ partial structure, which was readily attributed to C(19)–C(18) ethylidene side chain.

The C/D ring junction stereochemistry in **69** was determined to be *trans* from the observation of the diagnostic Wenkert-Bohlmann bands (*vide supra*) in the IR spectrum,[355,356] which was also in agreement with the reciprocal NOEs observed for H(3), H(5α)/H(21α) (Figure 2.94). The orientation of H(3) was assigned as α (C(3) is *S*) from the NOEs observed, as well as from the observed $J_{3\text{-}14\beta}$ value of 12 Hz, which require H(3) and H(14β) to be in a *trans*-diaxial arrangement. The configuration at the spirocyclic carbon C(7) was determined by comparison with the chemical shifts of the related corynanthean-type oxindole alkaloids.[360,362-366] The marked differences in the ^{13}C NMR data of the 3(*S*), 7(*R*)- and 3(*S*), 7(*S*)-stereoisomers, which involve the carbon shifts of C(3) and C(9), provide a diagnostic tool for the determination of the C(7)-spirocarbon configuration.[362-366] The carbon resonances of C(3) in the 3(*S*), 7(*R*)-

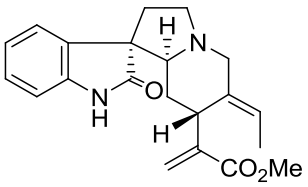
oxindoles are consistently *ca.* 2 to 3 ppm lower field than those in the 3(*S*), 7(*S*) counterparts, while the C(9) resonances in the 3(*S*), 7(*R*)-oxindoles are consistently *ca.* 2 to 3 ppm higher field than those in the 3(*S*), 7(*S*) counterparts. The chemical shifts of C(3) and C(9) in **69** (δ 70.4 and 125.1, respectively) were found to be consistent with a 7(*S*) configuration. This was also supported by the observed reciprocal NOEs between H(9)/H(5β), H(6β), and H(14β) as shown in Figure 2.94.

2.2.3.2 Compound 70

Compound **70** was obtained as a light yellowish oil, $[\alpha]_D$ +38 ($CHCl_3$, *c* 0.08). The UV and IR spectra were similar to those of **69**. The ESIMS of **70** showed a quasi molecular ion at *m/z* 353, and HRESIMS measurements established the molecular formula as $C_{21}H_{24}N_2O_3$ (DBE 11), indicating that compound **70** is isomeric with **69**.



69



70

The NMR spectroscopic data of **70** (Tables 2.46 and 2.47) were similar in all respects to those of **69**, except for the chemical shifts of H(15) and C(15), suggesting that compound **70** is the C(15) epimer of **69**. The 15(*R*) configuration of **70** can be readily verified by NOE experiments (Figure 2.95). In compound **70**, NOEs were observed for H(17a)/H(21α), while NOEs for H(3)/H(15) and H(15)/H(21α) were not seen. These observations are consistent only with an α-methyl methacrylate substitution (or an

axially oriented methyl methacrylate) at C(15). In the converse case (15(*S*)), H(17a) and H(21α) will be too far apart for NOEs to be observed. Moreover, in the ^{1}H NMR spectrum (Figure 2.98) of **70**, the chemical shift of H(15) was relatively deshielded (δ 3.78) compared to the chemical shift of H(15) in **69** (δ 3.30). This is attributed to paramagnetic deshielding caused by the proximity of the C(20)–C(19) double bond (ethylidene side chain at C(20)).

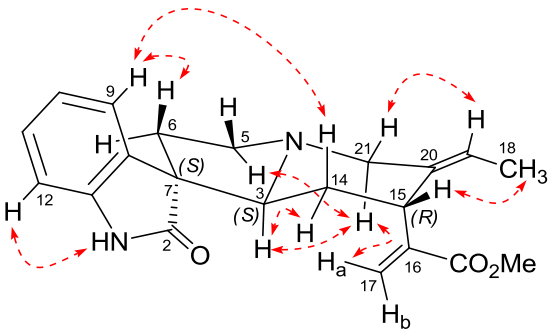
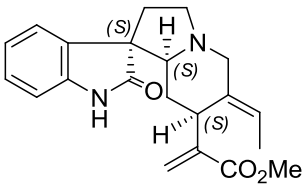


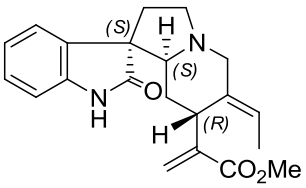
Figure 2.95: Selected NOEs of **70**

2.2.3.3 Compound 71

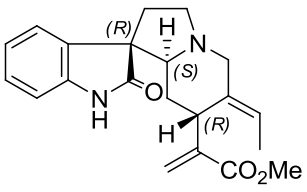
Compound **71** was obtained as a light yellowish oil with $[\alpha]_D$ +42 ($CHCl_3$, *c* 0.41). The UV and IR spectra were similar to those of **70**, suggesting a corynanthean oxindole with similar functionalities. The ESIMS of **71** showed an $[M + H]^+$ peak at *m/z* 353, and HRESIMS measurements established the molecular formula as $C_{21}H_{24}N_2O_3$, indicating that compound **71** is isomeric with **69** and **70**.



69



70



71

The NMR spectroscopic data of **71** (Tables 2.46 and 2.47) were very similar to those of **70**, except for the chemical shifts of C(3) and C(9), and some key NOEs. This suggested that compound **71** is the C(7) epimer of **70**. The 7(*R*) configuration of **71** can be determined by comparison of the H(9) chemical shift with those of oxindoles belonging to the 7(*S*) series (**69**–**70** and **72**). In the 7(*S*) oxindoles, **69**, **70** and **72**, the chemical shifts of H(9) were observed at δ 7.41, 7.34, and 7.35, respectively, due to the close proximity of H(9) with the *N*(4) lone pair. However, the chemical shift of H(9) was found to be relatively more shielded (δ 7.14) in the case of **71**, indicating the opposite configuration, *i.e.*, *R*, at C(7).[366] This was supported by NOE experiments (Figure 2.96), which showed reciprocal NOEs for H(9)/H(3), H(6α), whereas these NOEs were not observed in **69**, **70**, and **72**. The relative configurations at other stereogenic centers in **71** were similar to those in **70** from examination of the NOE data (Figure 2.96).

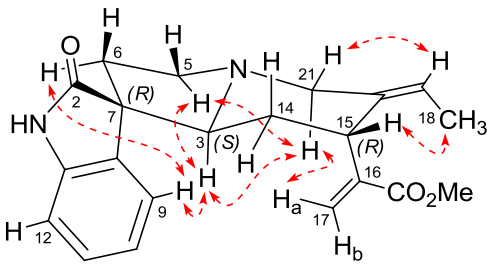


Figure 2.96: Selected NOEs of **71**

Table 2.46: ^{1}H NMR Spectroscopic Data of Compounds **69**–**71**[a]

H	**69**	**70**	**71**
3	2.93 dd (12, 3.2)	2.59 dd (11, 3.2)	2.40 m
5α	2.74 dd (15.4, 8.3)	2.47 dd (17, 8.6)	2.43 m
5β	3.21 m	3.30 td (8.6, 2)	3.35 m
6β	2.03 m	2.03 dt (13, 8.6)	1.99 m (α)
6α	2.44 ddd (13, 8.3, 4.5)	2.36 ddd (13, 8.6, 2)	2.46 m (β)
9	7.34 d (7.5)	7.35 br d (7.7)	7.14 dd (7.5, 1)
10	7.01 t (7.5)	6.98 td (7.7, 1)	6.99 td (7.5, 1)
11	7.18 t (7.5)	7.15 td (7.7, 1)	7.15 td (7.5, 1)
12	6.88 d (7.5)	6.83 br d (7.7)	6.88 dd (7.5, 1)
14β	1.29 m	1.31 m	1.50 m
14α	1.36 m	1.36 m	1.86 td (13, 6)
15	3.30 br d (9)	3.78 br d (5.4)	3.87 br d (6)
17a	5.42 s	5.47 s	5.35 s
17b	6.13 s	6.16 s	6.03 s
18	1.43 d (7)	1.49 dd (7, 2)	1.53 dd (6.8, 1.5)
19	5.45 q (7)	5.59 q (7)	5.60 q (6.8)
21α	2.98 d (12)	2.98 d (12)	2.85 d (12)
21β	3.51 d (12)	3.55 d (12)	3.59 d (12)
NH	8.79 br s	8.28 br s	8.83 br s
CO_2*Me*	3.69 s	3.67 s	3.54 s

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HSQC, and NOESY/DNOE.

Table 2.47: ^{13}C NMR Spectroscopic Data of Compounds **69**–**71**[a]

C	**69**	**70**	**71**
2	181.8	181.8	181.9
3	70.4	67.6	70.3
5	54.0	54.4	55.0
6	36.2	35.4	35.0
7	57.1	56.6	55.8
8	133.2	133.4	133.1
9	125.1	125.3	124.1
10	122.5	122.5	122.6
11	127.8	127.7	128.0
12	109.8	109.6	109.9
13	140.4	140.2	141.2
14	32.1	29.4	28.2
15	40.6	34.7	35.0
16	143.2	140.9	141.4
17	125.3	126.3	125.3
18	13.9	13.0	13.0
19	121.6	123.3	122.9
20	135.2	134.0	133.4
21	61.7	60.0	59.4
CO_2*Me*	52.0	51.9	51.9
CO_2Me	167.4	167.6	168.0

[a] $CDCl_3$, 100 MHz; assignments based on HSQC and HMBC.

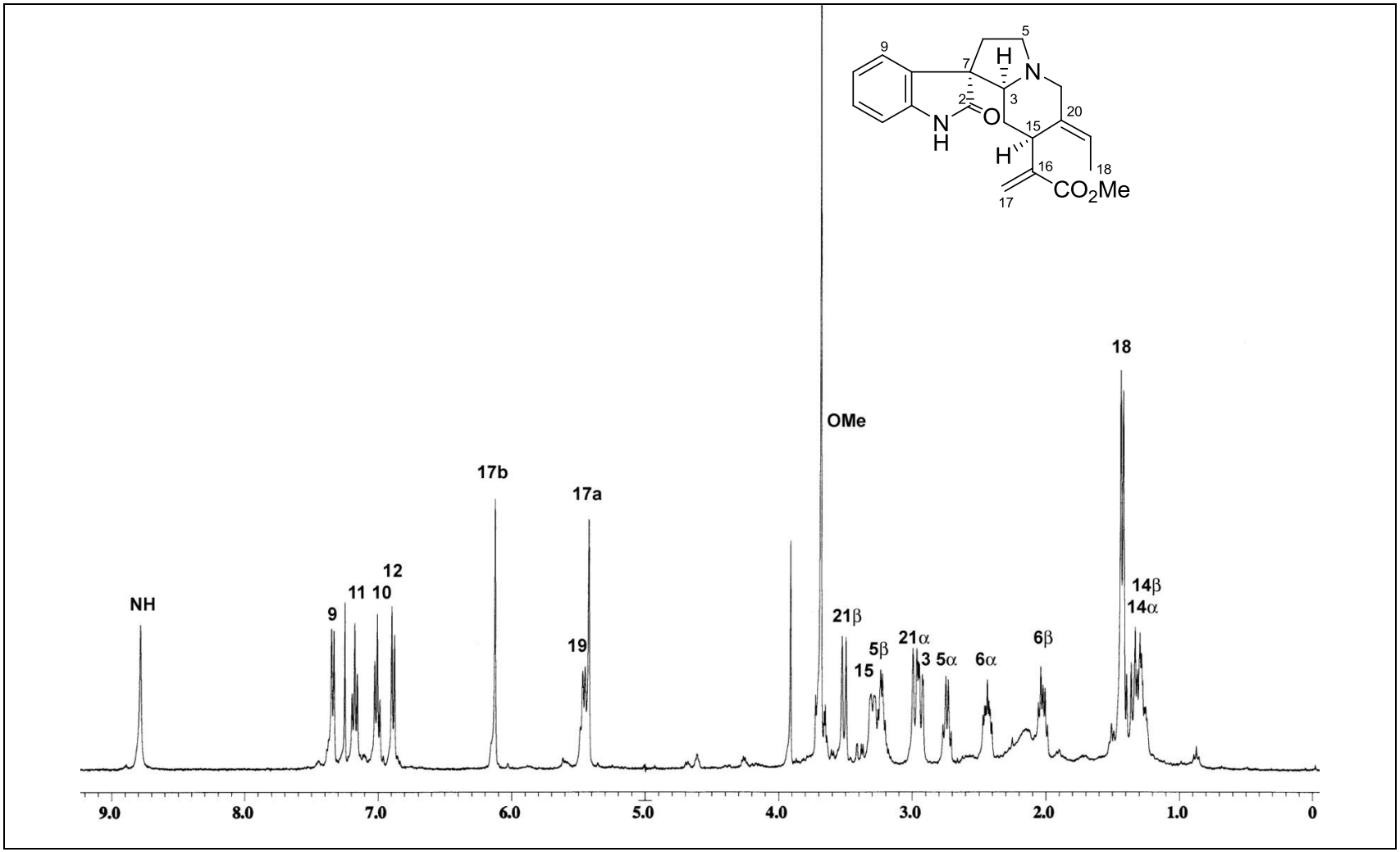


Figure 2.97: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of compound **69**

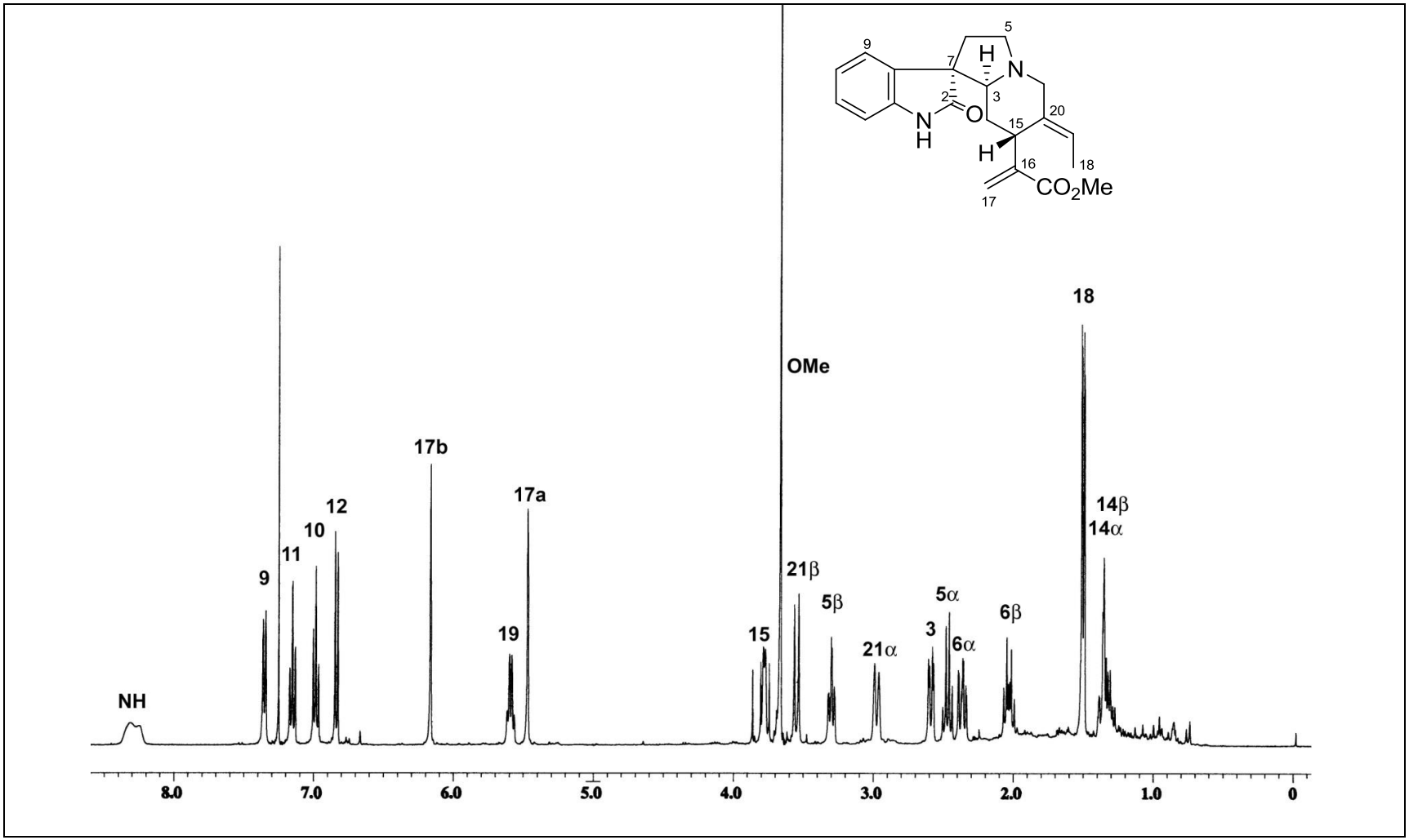


Figure 2.98: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of compound **70**

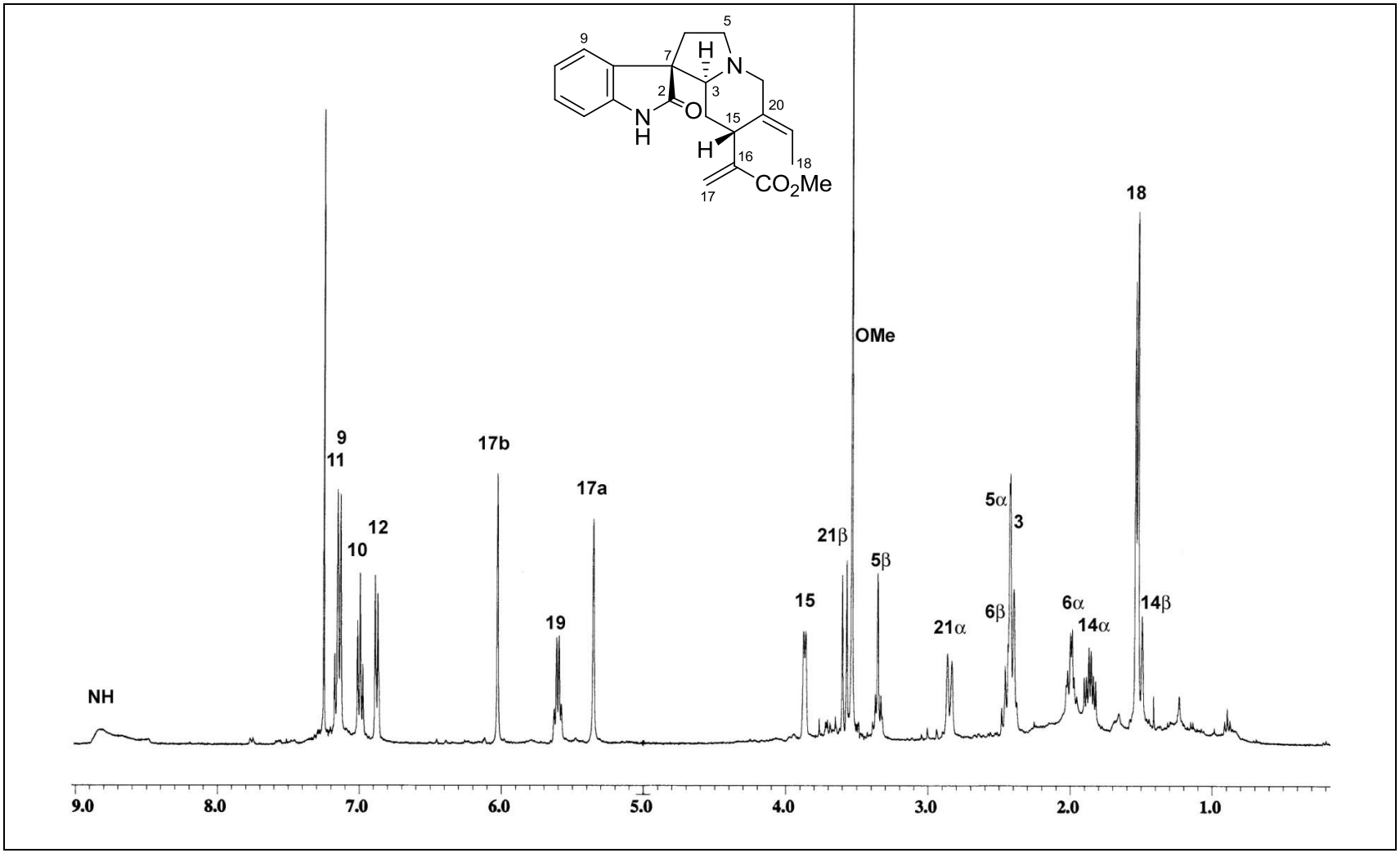


Figure 2.99: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of compound **71**

2.2.3.4 (–)-Catharinensine (72)

The only known corynanthean-type oxindole alkaloid isolated from *K. pauciflora* is (–)-catharinensine (**72**).[359] The ^{1}H NMR spectrum of this compound is shown in Figure 2.100, while the complete assignments of the NMR spectroscopic data of this compound are summarized in Table 2.48. Other data are given in the Experimental Section.

Table 2.48: ^{1}H and ^{13}C NMR Spectroscopic Data of Catharinensine (**72**)[a]

Position	δ_H	δ_C
2	–	181.9
3	2.54 dd (11.3, 2.7)	72.0
5α	2.52 m	53.5
5β	3.24 m	
6β	2.03 m	35.0
6α	2.38 ddd (13, 9.5, 2.7)	
7	–	57.3
8	–	134.2
9	7.41 br d (7.7)	124.8
10	7.04 td (7.7, 1.3)	122.6
11	7.20 td (7.7, 1.3)	127.6
12	6.91 br d (7.7)	109.7
13	–	140.2
14β	0.98 m	25.1
14α	1.02 m	
15	2.73 br d (13)	40.6
16	–	142.6
17a	5.03 s	124.5
17b	6.07 s	
18	0.84 t (7)	12.8
19	0.97 m	18.4
	1.45 m	
20	1.70 m	37.9
21α	2.22 dd (11, 2.3)	54.7
21β	3.23 m	
NH	8.69 br s	–
CO_2*Me*	3.71 s	51.9
CO_2Me	–	167.6

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY/DNOE.

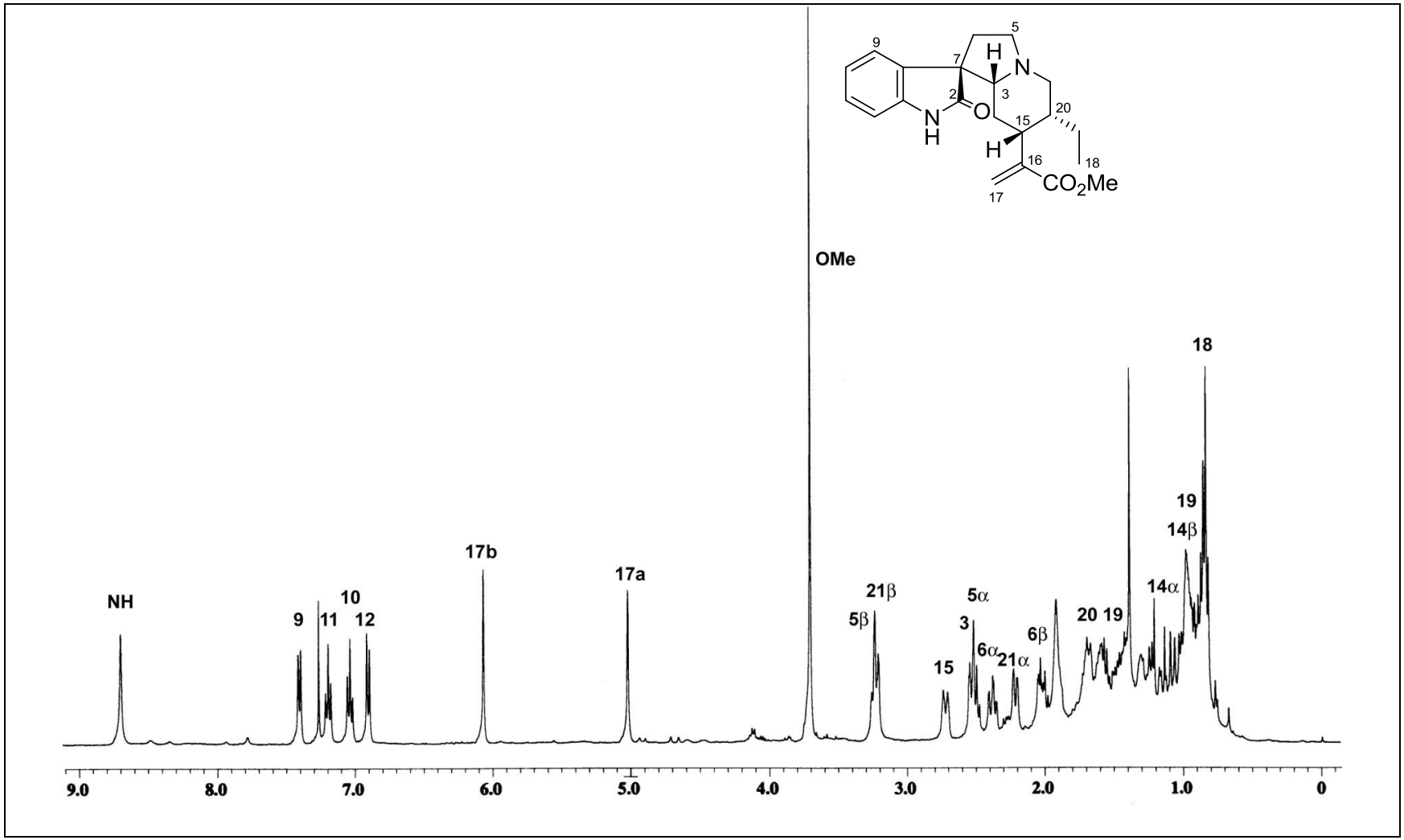
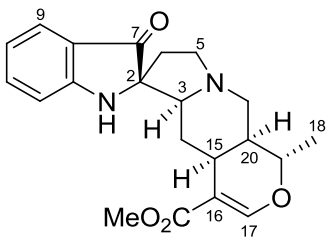


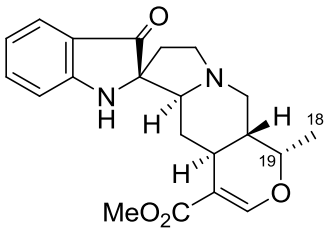
Figure 2.100: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of catharinensine (**72**)

2.2.3.5 Tetrahydroalstonine pseudoindoxyl (73)

Tetrahydroalstonine pseudoindoxyl (**73**) was obtained as a light yellowish oil with $[\alpha]_D$ –196 ($CHCl_3$, *c* 0.16). The IR spectrum indicated the presence of NH (3351 cm^{-1}), ketone (1703 cm^{-1}), and ester (1621 cm^{-1}) functions, while the UV spectrum showed absorption maxima at 208 and 235 nm, characteristic of a pseudoindoxyl chromophore.[357,367] The ESIMS showed an $[M + H]^+$ peak at *m/z* 369, and HRESIMS measurements established the molecular formula as $C_{21}H_{24}N_2O_4$. The ^{13}C NMR data (Table 2.49) showed a total of 21 carbon resonances, comprising two methyl, four methylene, nine methine, and six quaternary carbons, in agreement with the molecular formula.



73



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The ^1H and ^{13}C NMR data (Table 2.49) of **73** showed a general similarity to those of ajmalicine pseudoindoxyl (**473**),[368] except for some differences. In the ^1H NMR spectrum of ajmalicine pseudoindoxyl (**473**),[368] H(19) was observed at δ 4.36 as a quartet of doublets (*J* = 6.6, 3.5 Hz), while H(19) of **73** was seen at δ 4.41 as a doublet of quartets (*J* = 10.4, 5.9 Hz), suggesting that H(19) and H(20) in **73** are in a *trans*-

diaxial arrangement. This observation requires H(20) in **73** to be α-oriented (*cis* D/E ring junction), instead of a β-oriented H(20) in **473** (*trans* D/E ring junction).

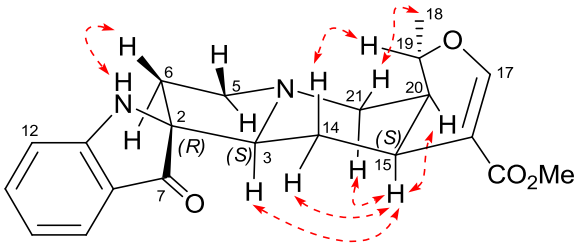


Figure 2.101: Selected NOEs of **73**

In order to confirm this deduction, NOE experiments were carried out. Reciprocal NOEs were observed between H(14β) and H(19). These NOEs are only possible if the D/E ring junction is *cis*, with H(20) α-oriented (Figure 2.101). In addition, irradiation of H(15) resulted in enhancement of the H(3), H(14α), H(20), and H(21α) signals, providing further confirmation for the assignment of the configuration at C(20) as *S* (α-oriented H(20)). The configuration at C(2) was assigned as *R*, from the observed reciprocal NOEs between the indolic NH and H(6β). This assignment also received additional support from examination of the chemical shift of the indolic NH in other corynanthean-type pseudoindoxyl alkaloids. The indolic NH resonances in all corynanthean-type pseudoindoxyl alkaloids with 2(*R*) configuration (or A configuration) are consistently observed above 5 ppm in the ^{1}H NMR spectrum, while the indolic NH in the 2(*S*) counterparts are observed below 5 ppm.[368] Compound **73** is therefore tetrahydroalstonine pseudoindoxyl (**73**), with an *allo* A configuration (*allo*: H(3), H(15), and H(20) on α-face; A configuration: carbonyl below C/D plane).[367,368] Although **73** is encountered as a natural product for the first time, an alkaloid corresponding to **73** was previously obtained during oxidative transformation of

tetrahydroalstonine as part of a larger study on the oxidative transformation of yohimbinoid alkaloids.[369]

Table 2.49: ^{1}H and ^{13}C NMR Spectroscopic Data of Tetrahydroalstonine pseudoindoxyl (**73**)[a]

Position	δ_H	δ_C	DNOE/NOESY
2	–	74.5	
3	2.39 m	71.4	15
5α	2.35 m	53.5	
5β	3.14 m		5α
6β	1.88 m	35.2	NH
6α	2.32 m		
7	–	202.2	
8	–	120.4	
9	7.56 br d (7.3)	124.7	10
10	6.77 td (7.3, 1)	118.5	9
11	7.42 td (7.3, 1)	137.5	12
12	6.80 br d (7.3)	111.7	11, NH
13	–	160.4	
14β	1.31 m	28.8	19
14α	1.70 dt (13, 4.5)		15
15	2.51 dt (12, 4.5)	30.2	3, 14α, 20, 21α
16	–	110.0	
17	7.47 s	155.1	
18	1.38 d (5.9)	18.7	20, 21β
19	4.41 dq (10.4, 5.9)	72.0	14β, 18
20	1.59 m	37.8	15, 18, 21α, 21β
21α	2.33 m	53.6	20, 21β
21β	3.22 d (11.8)		18, 21α
NH	5.04 br s	–	6β, 12
CO_2*Me*	3.60 s	51.2	
CO_2Me	–	167.7	

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY/DNOE.

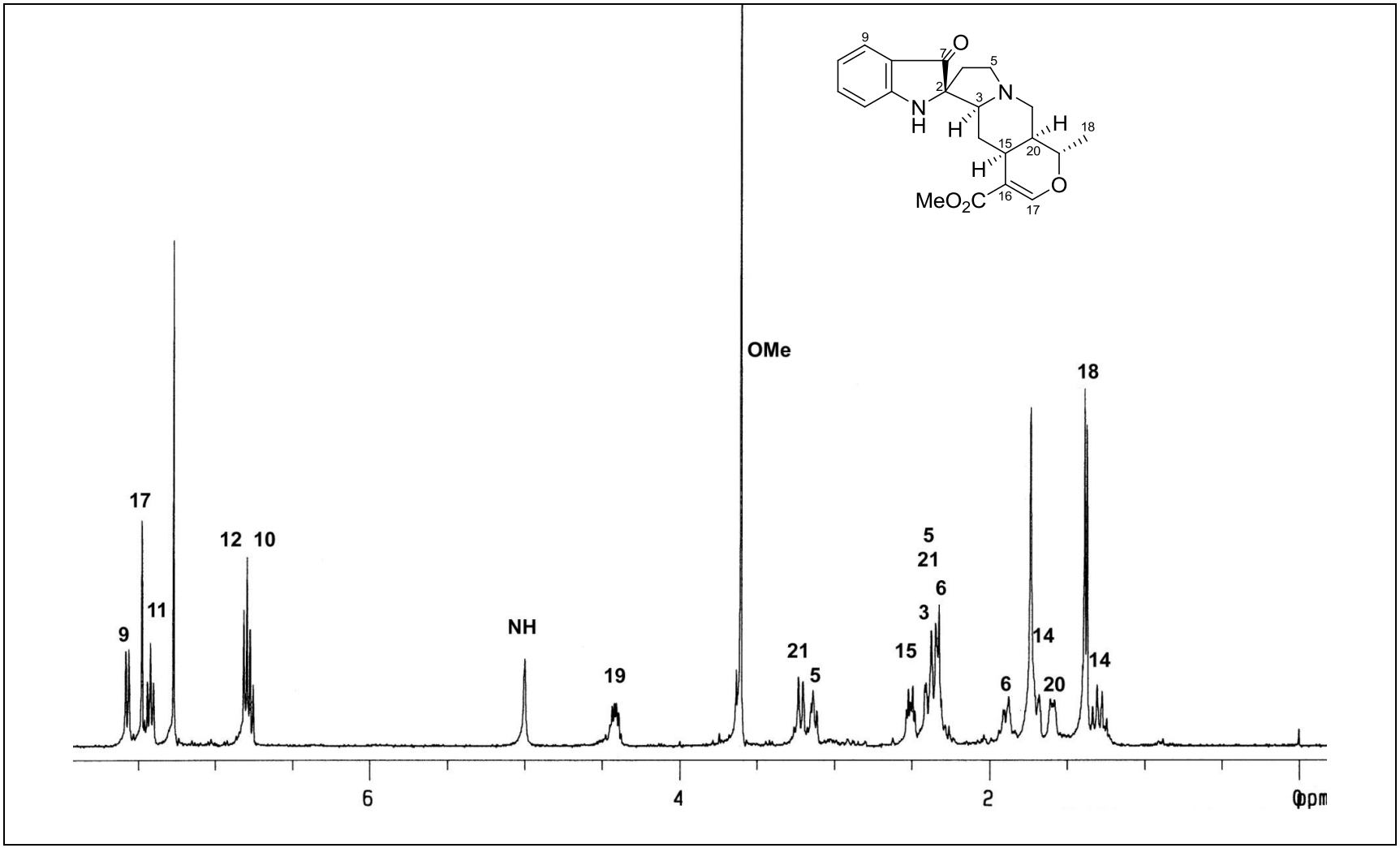


Figure 2.102: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of tetrahydroalstonine pseudoindoxyl (**73**)

2.2.3.6 Tetrahydroalstonine (43) and 16(*R*)-19,20-*E*-Isositsirikine (47)

Two known alkaloids belonging to this group, *viz.*, tetrahydroalstonine (**43**)[188] and 16(*R*)-19,20-*E*-isositsirikine (**47**)[335-337] were also isolated. These compounds were also obtained from *L. griffithii*. Their NMR spectroscopic data are presented in the previous section (section 2.1.6.1). Other data are given in the Experimental Section.

2.2.4 *Aspidosperma* Alkaloids

2.2.4.1 (+)-Aspidospermidine (74), (+)-1,2-Dehydroaspidospermidine (75), and (−)-Quebrachamine (76)

Three known alkaloids belonging to this group, *viz.*, (+)-aspidospermidine (**74**),[370-372] (+)-1,2-dehydroaspidospermidine (**75**),[370,372] and (−)-quebrachamine (**76**)[147,373] were also isolated. The ^{1}H NMR spectra of these compounds are shown in Figures 2.103–2.105, while the NMR spectroscopic data are summarized in Tables 2.50 and 2.51. Other data are given in the Experimental Section.

Table 2.50: ^{1}H NMR Spectroscopic Data of (+)-Aspidospermidine (**74**), (+)-1,2-Dehydroaspidospermidine (**75**), and (−)-Quebrachamine (**76**)[a]

H	**74**	**75**	**76**
2	3.53 br s	–	–
3	1.98 m	2.20 m	2.26 td (11.3, 3.2)
	3.09 m	3.17 m	2.45 m
5	2.28 m	2.60 ddd (11.3, 8.3, 5.5)	2.34 td (11, 4.5)
	3.14 m	3.19 m	2.42 m
6	1.47 m	1.65 dd (12, 5.5)	2.85 ddd (14.5, 4.5, 3.2)
	2.33 m	2.16 m	2.95 ddd (14.5, 11, 4.5)
9	7.08 br d (7.7)	7.33 d (7.7)	7.49 dd (7, 2)
10	6.73 td (7.7, 1)	7.16 t (7.7)	7.07 td (7, 2)
11	7.01 td (7.7, 1)	7.28 t (7.7)	7.27 td (7, 2)
12	6.63 br d (7.7)	7.51 d (7.7)	7.09 dd (7, 2)
14	1.53 m	1.56 m	1.31 m
	1.77 m	1.86 qt (13, 5)	1.59 m
15	1.11 td (14, 4.5)	1.00 td (13.6, 5)	1.14 m
	1.62 m	1.47 br dd (13, 3)	1.23 m
16	1.40 m	2.76 ddd (14, 10.6, 3)	2.69 m
	1.65 m	3.11 ddd (14, 12, 5)	2.69 m
17	1.06 m	1.60 m	1.62 m
	1.95 m	2.46 td (13, 3.2)	1.92 ddd (11.8, 7, 2.3)
18	0.63 t (7.2)	0.49 t (7.2)	0.86 t (7.4)
19	0.87 dq (14, 7.2)	0.62 m	1.14 m
	1.47 m	0.64 m	1.23 m
21	2.25 m	2.41 s	1.50 d (11.8)
			3.26 d (11.8)
NH	–	–	7.72 br s

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HSQC.

Table 2.51: ^{13}C NMR Spectroscopic Data of (+)-Aspidospermidine (**74**), (+)-1,2-Dehydroaspidospermidine (**75**), and (−)-Quebrachamine (**76**)[a]

C	**74**	**75**	**76**
2	65.7	192.5	140.0
3	54.0	52.1	55.2
5	53.1	54.6	53.3
6	38.9	35.2	22.5
7	53.4	61.3	108.7
8	135.8	147.1	129.0
9	122.9	121.1	117.5
10	119.1	125.2	118.8
11	127.2	127.6	110.1
12	110.5	120.2	120.3
13	149.5	154.5	134.9
14	21.8	22.1	22.8
15	34.5	33.3	34.9
16	28.2	23.8	22.0
17	23.1	27.3	33.5
18	6.9	7.4	7.9
19	30.1	29.8	32.1
20	35.8	36.6	37.2
21	71.4	79.1	56.8

[a] $CDCl_3$, 100 MHz; assignments based on HSQC and HMBC.

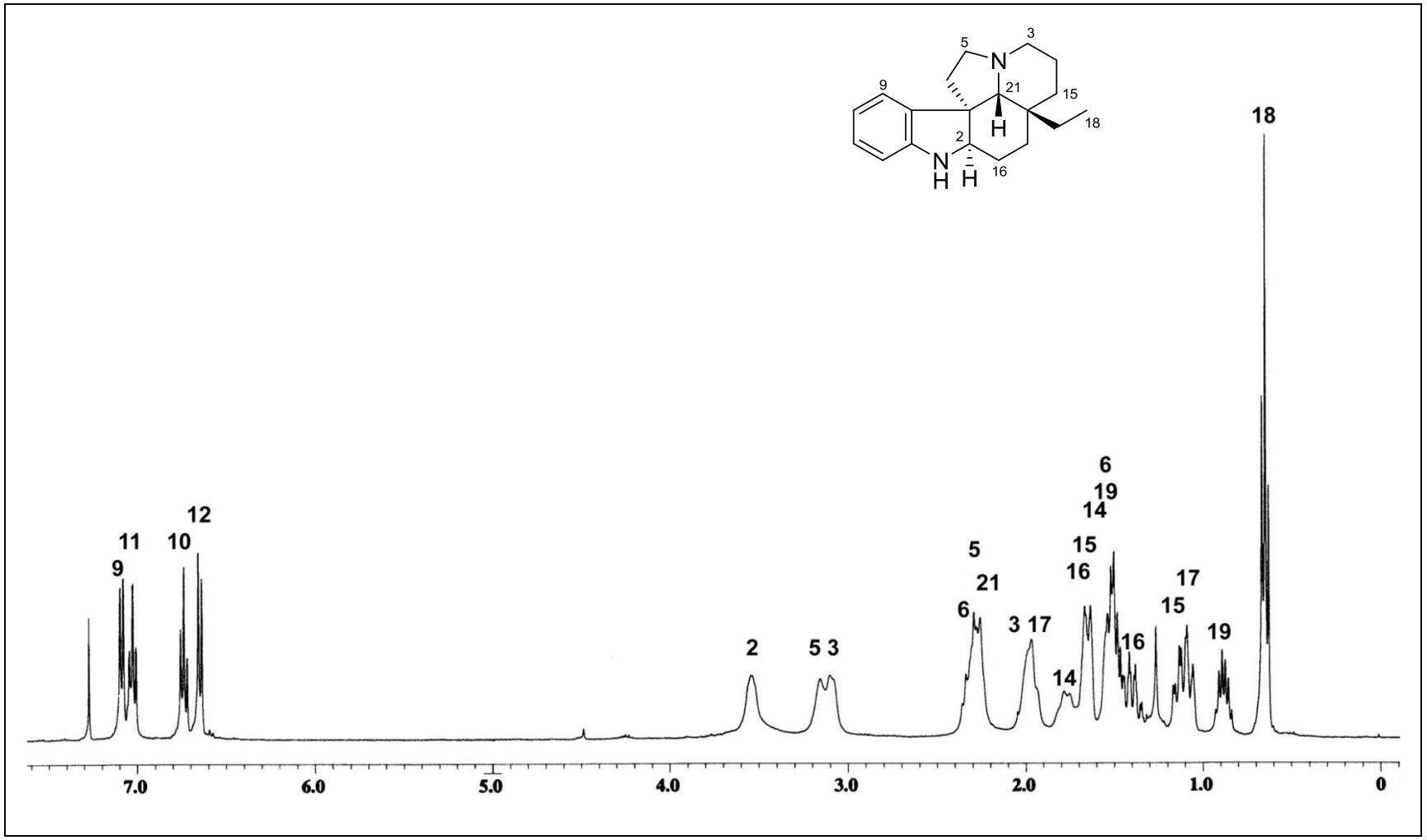


Figure 2.103: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (+)-aspidospermidine (**74**)

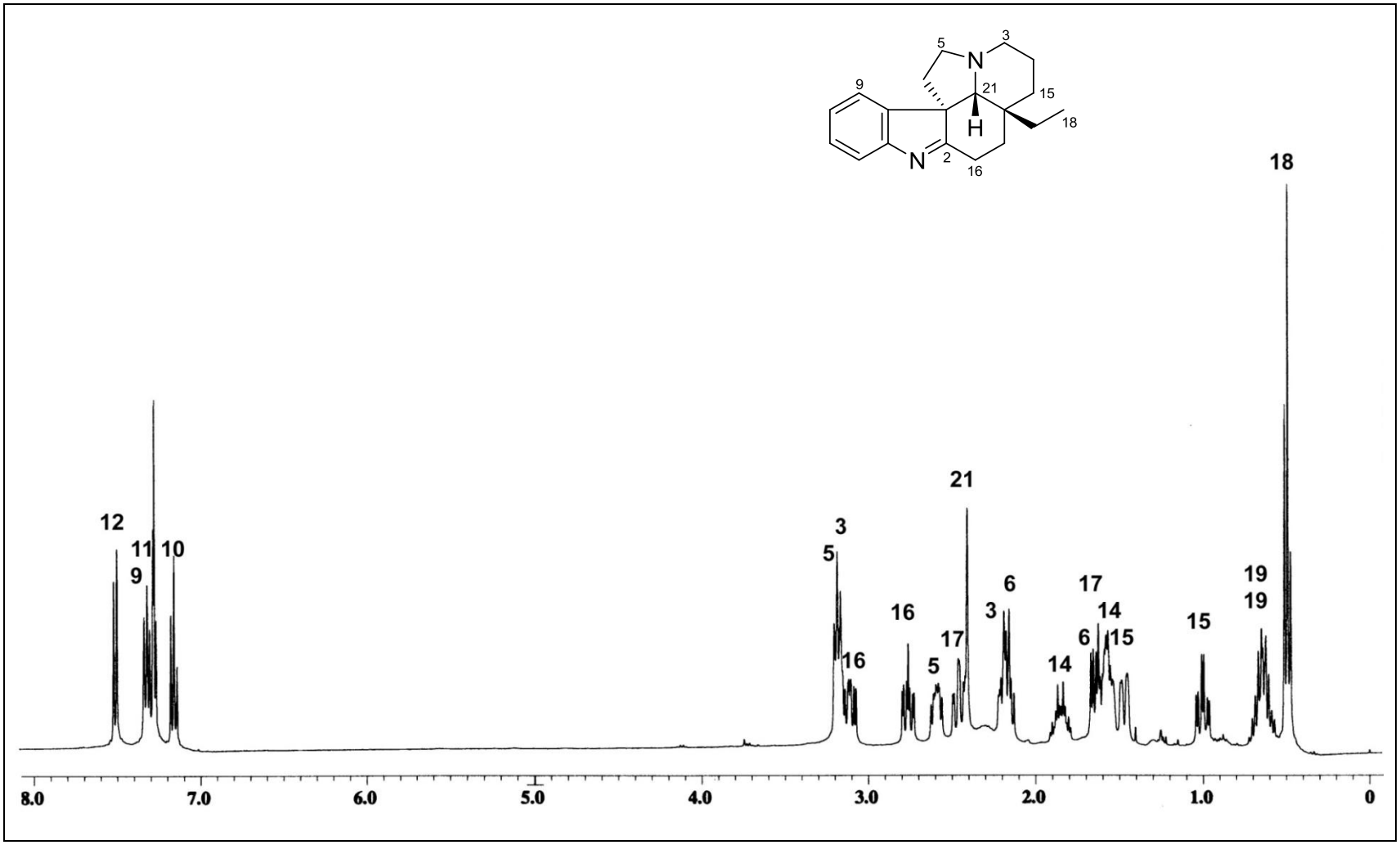


Figure 2.104: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (+)-1,2-dehydroaspidospermidine (**75**)

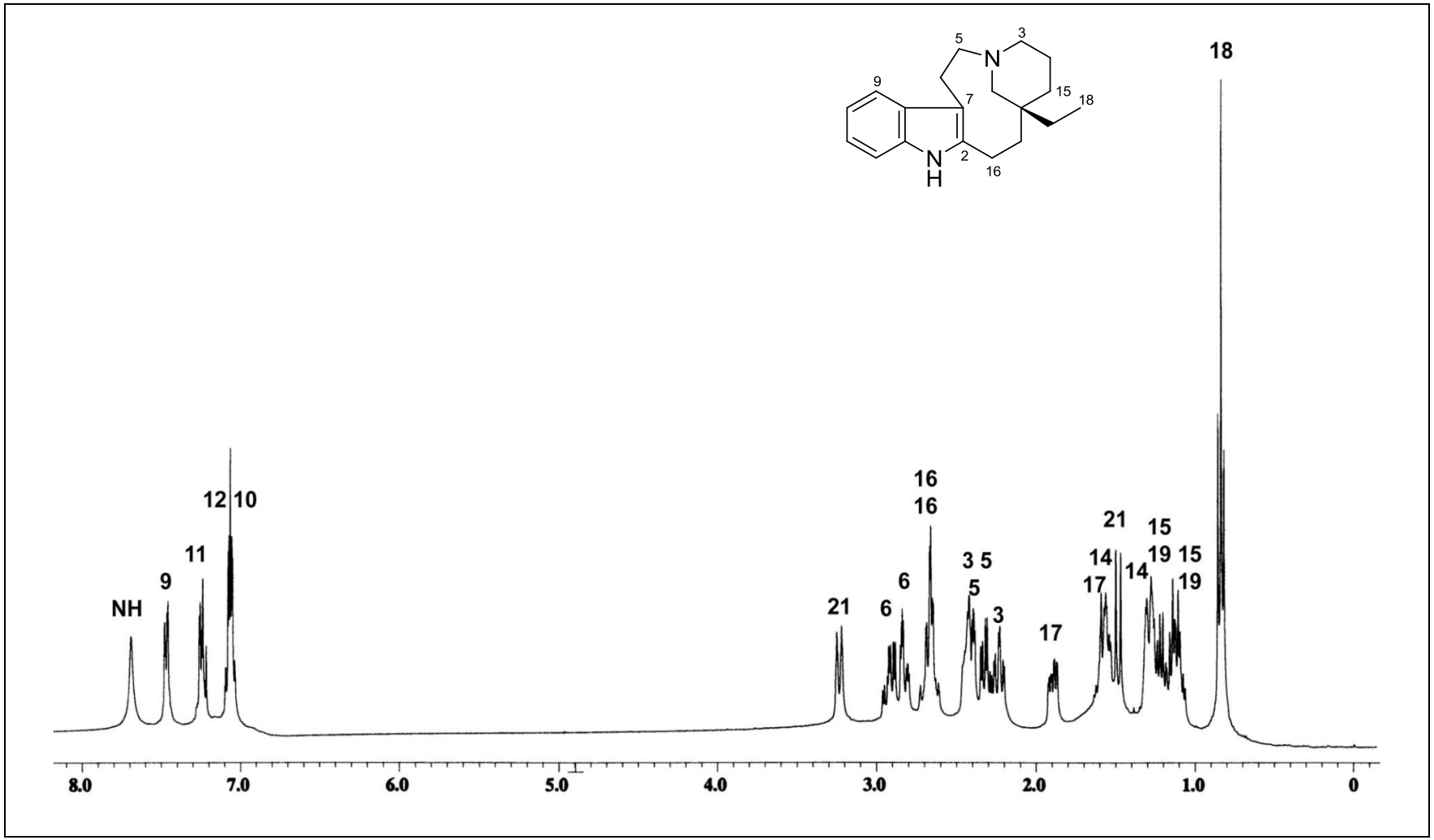
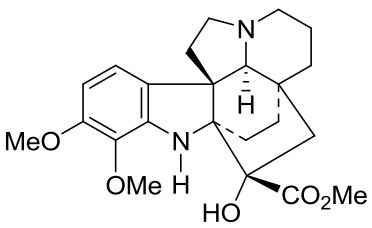


Figure 2.105: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (–)-quebrachamine (**76**)

2.2.5 Aspidofractinine Alkaloids

2.2.5.1 11,12-Dimethoxykopsinaline (77)

11,12-Dimethoxykopsinaline (**77**) was obtained as a light yellowish oil, $[\alpha]_D$ −18 ($CHCl_3$, *c* 0.11). The IR spectrum showed bands at 3490, 3349, and 1733 cm^{-1} due to OH, NH, and ester functions, respectively. The UV spectrum showed absorption maxima at 210, 250, and 293 nm, suggesting the presence of a dihydroindole chromophore. The ESIMS of **77** showed an $[M + H]^+$ peak at *m/z* 415, and HRESIMS measurements established the molecular formula as $C_{23}H_{30}N_2O_5$. The ^1H and ^{13}C NMR spectroscopic data of **77** (Table 2.52) were generally similar to those of the aspidofractinine alkaloid, 12-methoxykopsinaline (**222**),[147] except for the presence of an additional methoxy singlet (δ_H 3.79; δ_C 56.1) and the absence of one aromatic signal. The two aromatic doublets (δ_H 6.88 and 6.28) were readily assigned to H(9) and H(10), respectively, from the COSY spectrum. The placement of the OMe group at C(11) is consistent with the carbon resonance of C(11) at δ 151.8, which was further supported by the observed three-bond correlation from H(9) to C(11) in the HMBC spectrum. Compound **77** is therefore 11,12-dimethoxykopsinaline.



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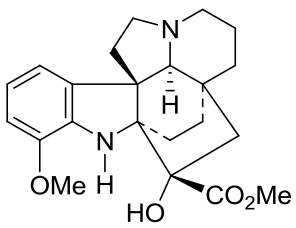


222

Table 2.52: ^{1}H and ^{13}C NMR Spectroscopic Data of 11,12-Dimethoxykopsinaline (**77**)[a]

Position	δ_H	δ_C
2	–	71.6
3	2.95 m	47.7
	3.10 br d (11.8)	
5	2.88 td (9, 2)	50.7
	3.25 m	
6	1.59 m	35.4
	2.39 m	
7	–	58.5
8	–	134.0
9	6.88 d (8.2)	116.7
10	6.28 d (8.2)	102.9
11	–	151.8
12	–	135.1
13	–	142.8
14	1.25 m	17.0
	1.86 m	
15	1.28 m	36.4
	1.71 m	
16	–	77.1
17	1.15 d (15)	40.9
	3.21 dd (15, 3)	
18	1.61 m	26.3
	1.75 m	
19	1.07 m	33.7
	1.49 m	
20	–	32.7
21	2.97 s	67.7
NH	4.45 br s	–
11-OMe	3.79 s	56.1
12-OMe	3.85 s	60.2
CO_2*Me*	3.80 s	52.3
CO_2Me	–	174.9

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HSQC, and HMBC.

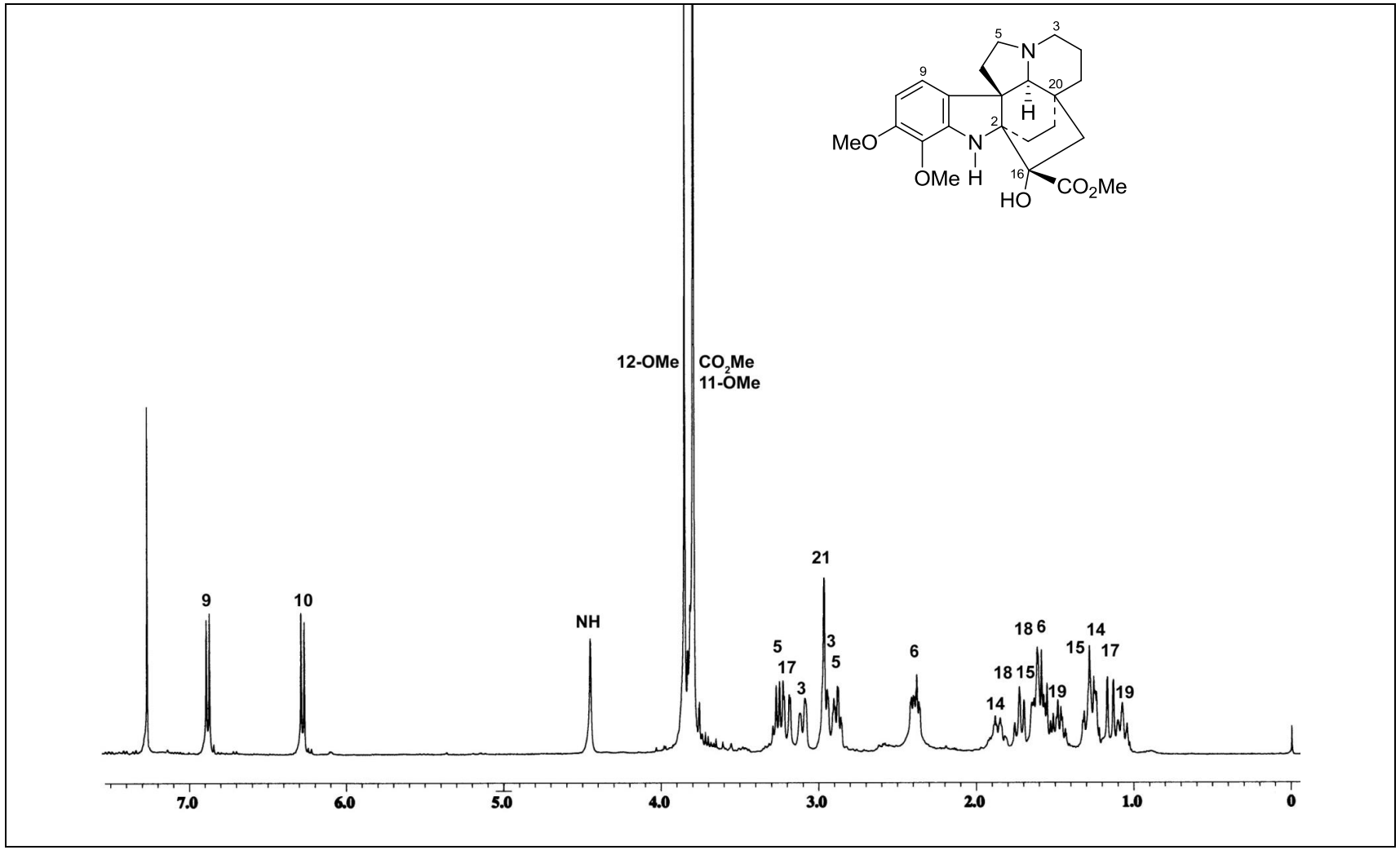


Figure 2.106: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 11,12-dimethoxykopsinaline (**77**)

2.2.5.2 Pseudokopsinine (78), Kopsinine (79), Kopsamine (80), *N*(1)-Decarbomethoxykopsamine (81), Kopsilongine (82), and Paucifinine (83)

Six known aspidofractinine alkaloids were obtained, *viz.*, pseudokopsinine (**78**),[374,375] kopsinine (**79**),[171,172] kopsamine (**80**),[171,172] *N*(1)-decarbomethoxykopsamine (**81**),[232] kopsilongine (**82**),[171,172] and paucifinine (**83**).[188] The ^{1}H NMR spectra of these compounds are shown in Figures 2.107–2.112. The NMR spectroscopic data of these compounds are summarized in Tables 2.53–2.56, while other data are given in the Experimental Section.

Table 2.53: ^{1}H NMR Spectroscopic Data of Pseudokopsinine (**78**) and Kopsinine (**79**)[a]

H	**78**	**79**
3	3.08 m	3.00 m
	3.08 m	3.12 ddt (14, 4, 2)
5	3.16 m	2.96 m
	3.33 td (8.6, 6.6)	3.35 q (8.3)
6	1.78 m	1.56 ddd (14, 8.3, 7.6)
	2.12 ddd (14.5, 6.8, 2.7)	2.64 ddd (14, 8.3, 3.4)
9	7.26 br d (7.5)	7.18 dd (7.5, 1)
10	6.85 td (7.5, 1)	6.75 td (7.5, 1)
11	7.06 td (7.5, 1)	6.99 td (7.5, 1)
12	6.77 br d (7.5)	6.66 br d (7.5)
14	1.56 m	1.23 m
	1.72 m	1.91 m
15	1.51 m	1.30 m
	1.51 m	1.61 m
16	3.03 m	2.89 td (9.3, 1)
17	1.75 m	1.37 m
	2.87 ddd (14, 6.4, 1.8)	2.78 ddd (13.7, 9.3, 3)
18	0.84 d (6.8)	1.42 m
		1.91 m
19	1.83 m	1.23 m
		1.41 m
21	3.18 d (1.3)	3.01 d (1.5)
NH	4.36 br s	3.75 br s
CO_2Me	3.69 s	3.76 s

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

Table 2.54: ^{13}C NMR Spectroscopic Data of Pseudokopsinine (**78**) and Kopsinine (**79**)[a]

C	**78**	**79**
2	80.6	66.4
3	48.1	47.4
5	55.0	50.5
6	37.2	34.5
7	60.3	57.7
8	140.1	140.4
9	123.7	121.4
10	121.3	119.5
11	127.3	126.4
12	112.8	110.6
13	149.5	148.9
14	20.6	16.9
15	28.9	36.3
16	40.2	43.6
17	31.2	31.9
18	7.5	33.6
19	51.0	33.7
20	44.6	31.5
21	78.7	68.1
CO_2*Me*	52.0	51.7
CO_2Me	175.1	174.6

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

Table 2.55: ^{1}H and ^{13}C NMR Spectroscopic Data of Kopsamine (**80**) and *N*(1)-Decarbomethoxykopsamine (**81**)[a]

Position	**80**		**81**	
	δ_H	δ_C	δ_H	δ_C
2	–	74.3	–	71.9
3	2.87 td (13, 3)	47.5	2.93 td (13, 3)	47.9
	3.05 m		3.11 dt (13, 2)	
5	2.94 td (8.5, 4)	50.2	2.88 td (8.5, 3.5)	50.7
	3.09 td (8.5, 7)		3.19 m	
6	1.63 m	36.7	1.54 m	35.6
	2.06 ddd (14.5, 8.5, 4)		2.26 ddd (14, 8.5, 3.5)	
7	–	57.5	–	58.5
8	–	134.1	–	130.9
9	6.76 d (7.8)	115.0	6.69 d (7.8)	114.4
10	6.52 d (7.8)	104.1	6.35 d (7.8)	101.1
11	–	148.2	–	147.4
12	–	136.2	–	137.9
13	–	123.1	–	133.2
14	1.25 m	17.0	1.29 m	17.4
	1.81 m		1.85 m	
15	1.27 td (14, 4)	35.0	1.30 m	36.1
	1.65 m		1.65 m	
16	–	74.5	–	76.9
17	1.40 dd (15, 1)	41.6	1.19 dd (15, 1.5)	40.9
	2.93 br d (15)		3.22 dd (15, 3)	
18	1.50 ddd (13, 11, 8)	23.7	1.72 ddd (13, 11, 8)	26.7
	2.34 ddd (13, 11, 1.5)		1.95 ddd (13, 11, 1.5)	
19	1.11 br t (11)	32.1	1.14 br t (11)	33.5
	1.69 m		1.54 m	
20	–	32.2	–	33.0
21	2.86 d (2)	67.9	2.95 d (1.5)	67.9
NH	–	–	4.12 s	–
CO_2*Me*	3.76 s	52.5	3.84 s	53.2
CO_2Me	–	173.0	–	174.8
NCO_2*Me*	3.88 s	53.2	–	–
N*C*O_2Me	–	156.1	–	–
OCH_2O	5.88 d (1.5)	100.2	5.85 d (1.5)	100.9
	5.90 d (1.5)		5.91 d (1.5)	
16-OH	6.98 s	–	–	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

Table 2.56: ^{1}H and ^{13}C NMR Spectroscopic Data of Kopsilongine (**82**) and Paucifinine (**83**)[a]

Position	**82**		**83**	
	δ_H	δ_C	δ_H	δ_C
2	–	74.6	–	74.6
3	2.86 td (13, 3)	47.6	2.81 m	43.0
	3.05 m		3.15 m	
5	2.95 m	50.3	3.01 m	47.7
	3.08 m		3.15 m	
6	1.76 m	37.0	1.65 m	36.6
	2.21 ddd (14.5, 8.5, 4)		2.05 m	
7	–	58.1	–	59.7
8	–	142.9	–	131.9
9	6.91 dd (7.5, 1)	114.5	6.75 br d (8)	116.3
10	6.99 t (7.5)	124.9	6.54 d (8)	103.8
11	6.77 dd (7.5, 1)	111.6	–	148.4
12	–	148.1	–	134.8
13	–	129.2	–	124.1
14	1.25 m	17.6	1.25 m	17.4
	1.81 m		1.76 m	
15	1.25 m	35.7	1.46 m	30.3
	1.64 m		1.70 m	
16	–	75.0	–	75.2
17	1.41 dd (15, 1)	41.9	1.56 br d (15)	41.8
	2.94 br d (15)		2.95 br d (15)	
18	1.47 ddd (13, 11, 8)	24.5	1.67 m	23.8
	2.37 ddd (13, 11, 1.5)		2.29 m	
19	1.06 br t (11)	32.1	1.65 m	28.9
	1.66 m		1.65 m	
20	–	32.4	–	36.4
21	2.83 d (1.5)	67.9	–	90.6
CO_2*Me*	3.76 s	52.3	3.75 s	52.5
CO_2Me	–	173.2	–	173.0
NCO_2*Me*	3.88 s	53.0	3.88 s	53.2
N*C*O_2Me	–	157.3	–	155.9
OCH_2O	–	–	5.87 d (1.5)	100.3
			5.93 d (1.5)	
12-OMe	3.82 s	56.2	–	–
16-OH	6.66 s	–	6.98 s	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

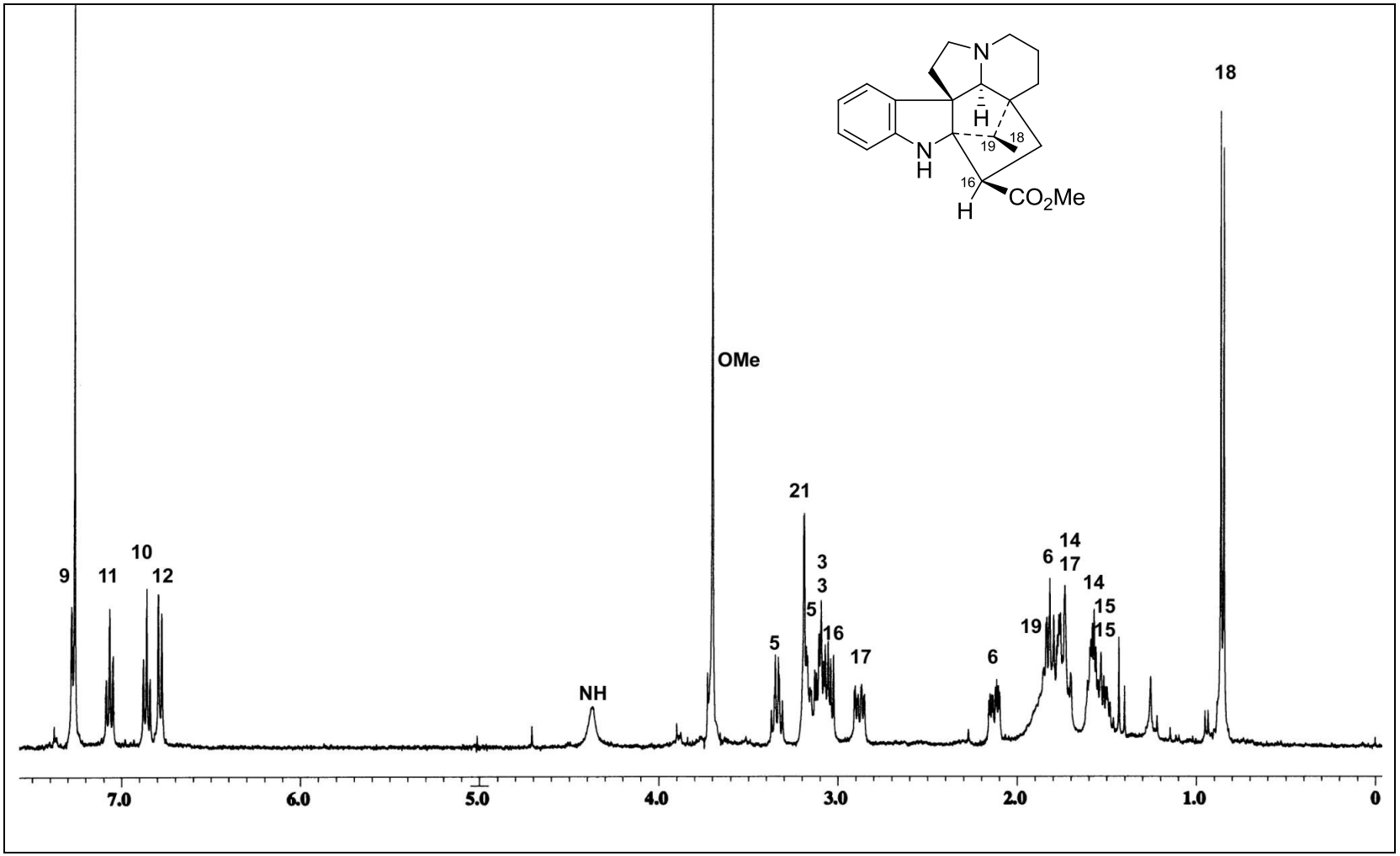


Figure 2.107: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of pseudokopsinine (**78**)

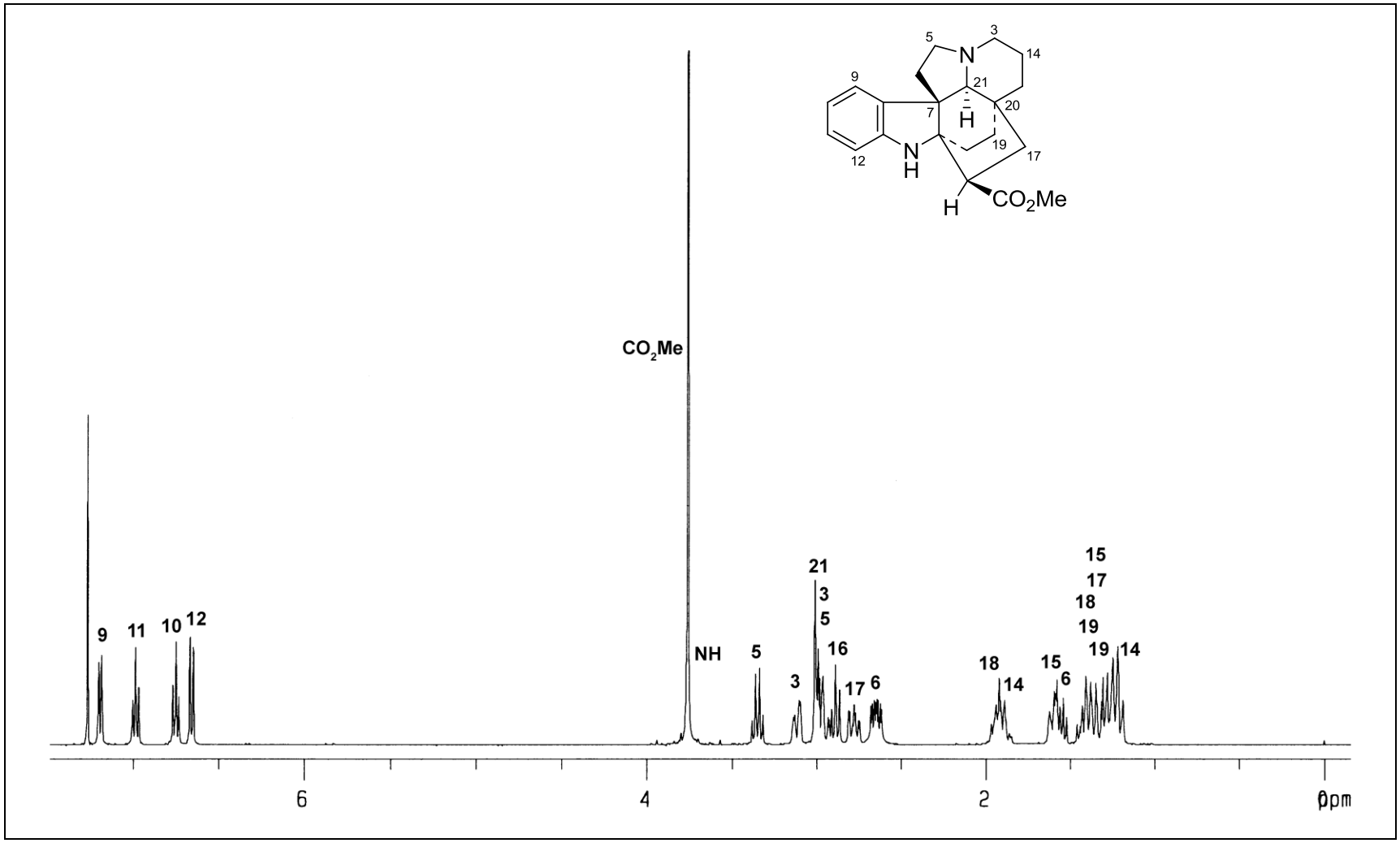


Figure 2.108: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of kopsinine (**79**)

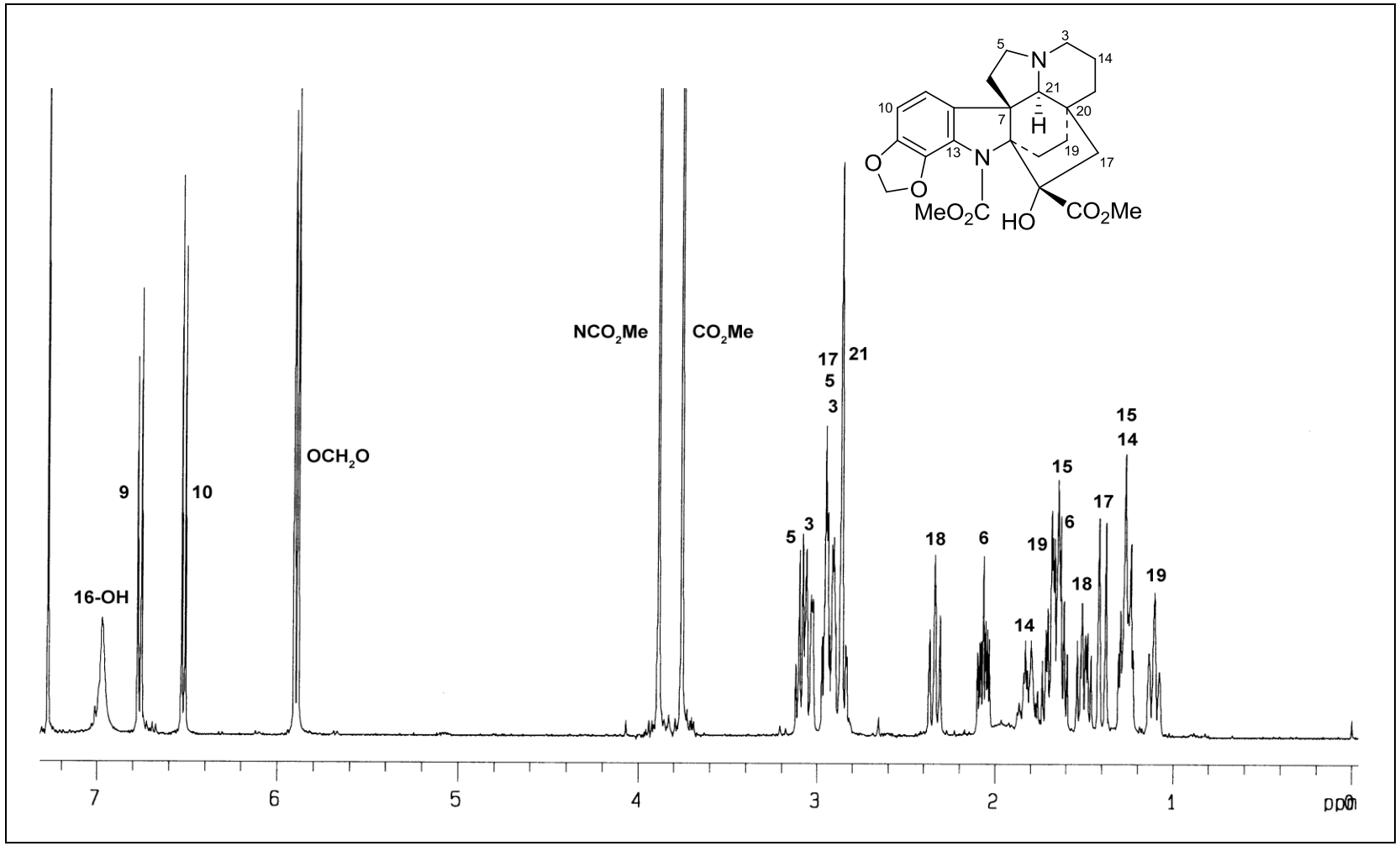


Figure 2.109: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of kopsamine (**80**)

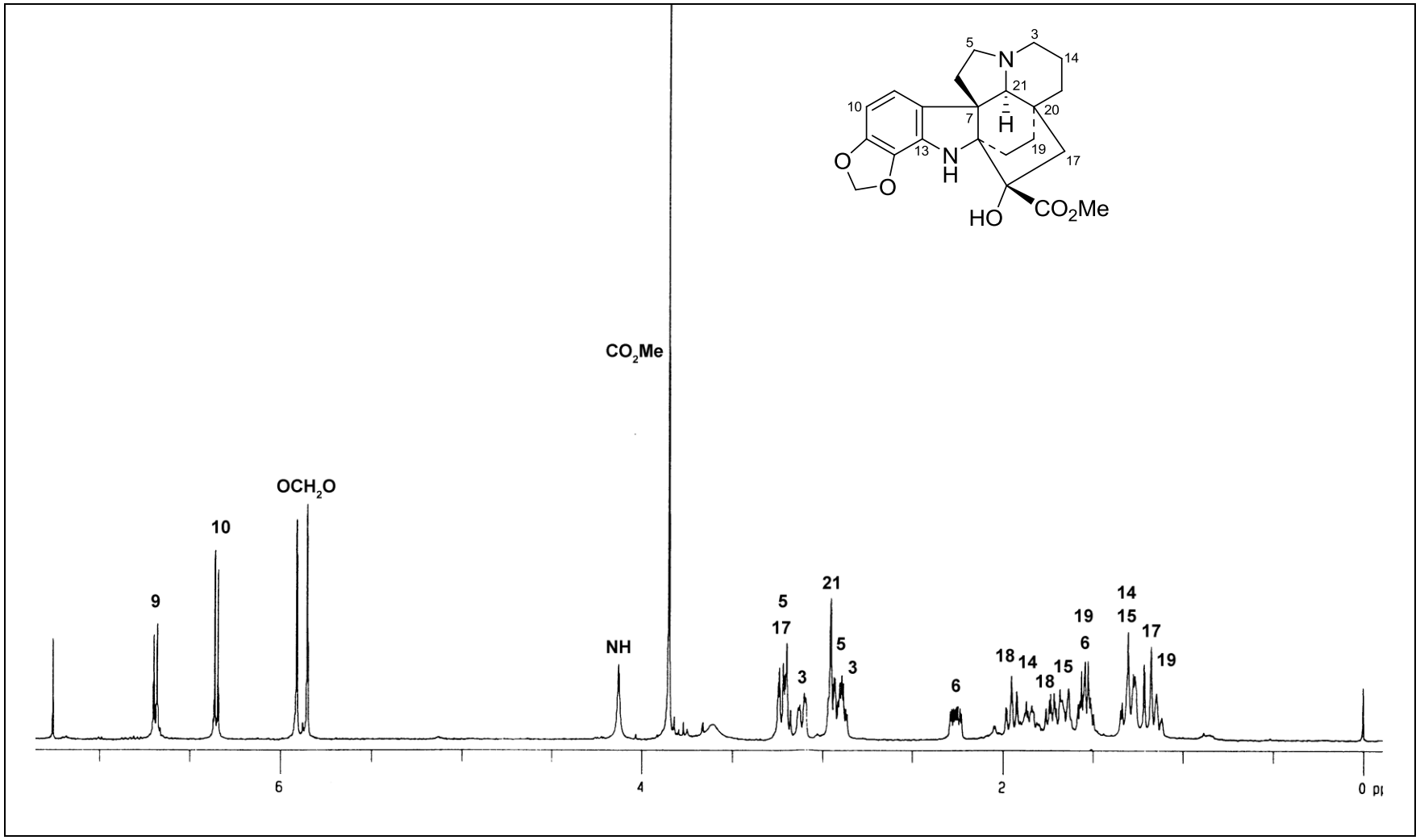


Figure 2.110: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *N*(1)-decarbomethoxykopsamine (**81**)

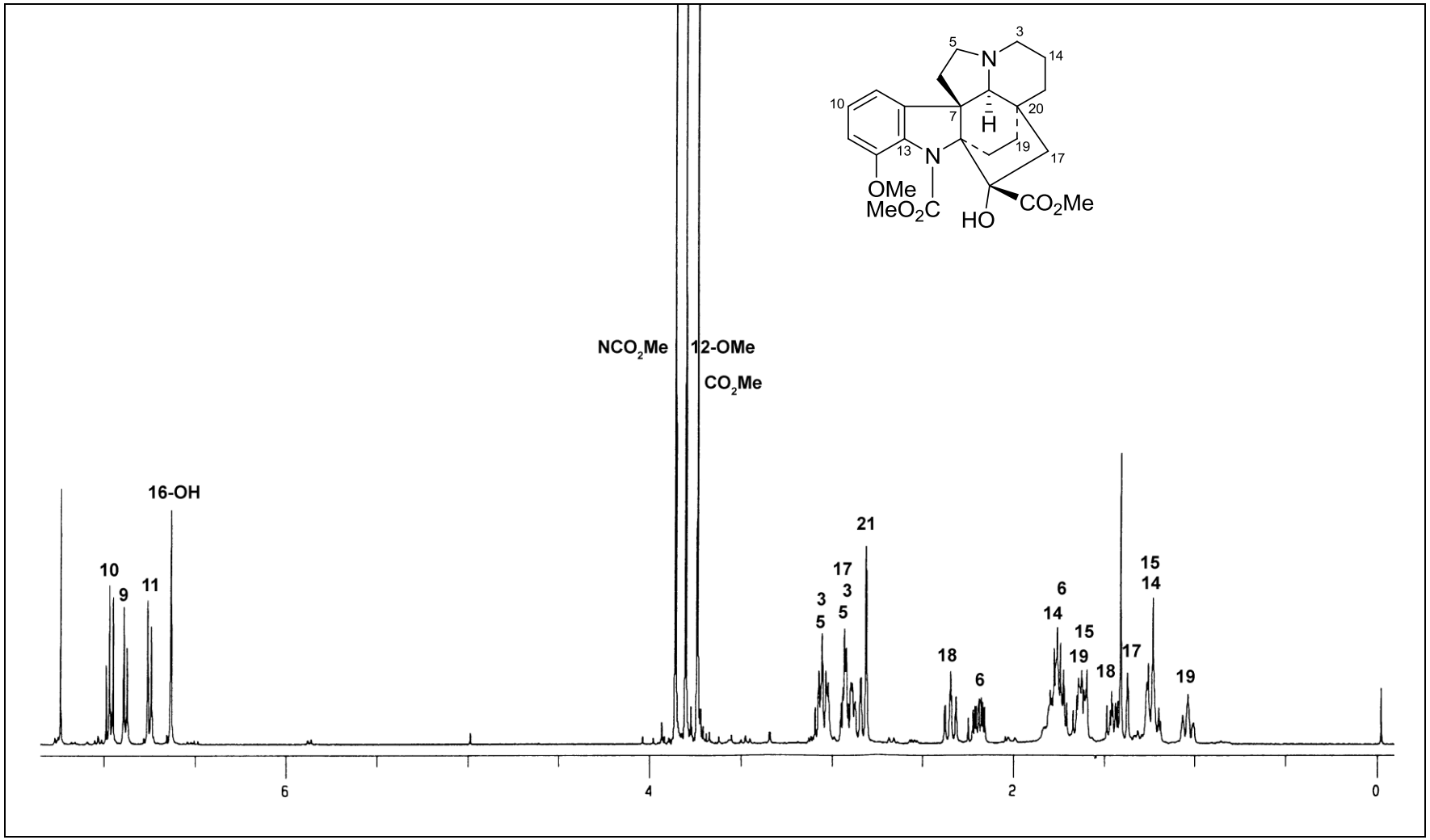


Figure 2.111: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of kopsilongine (**82**)

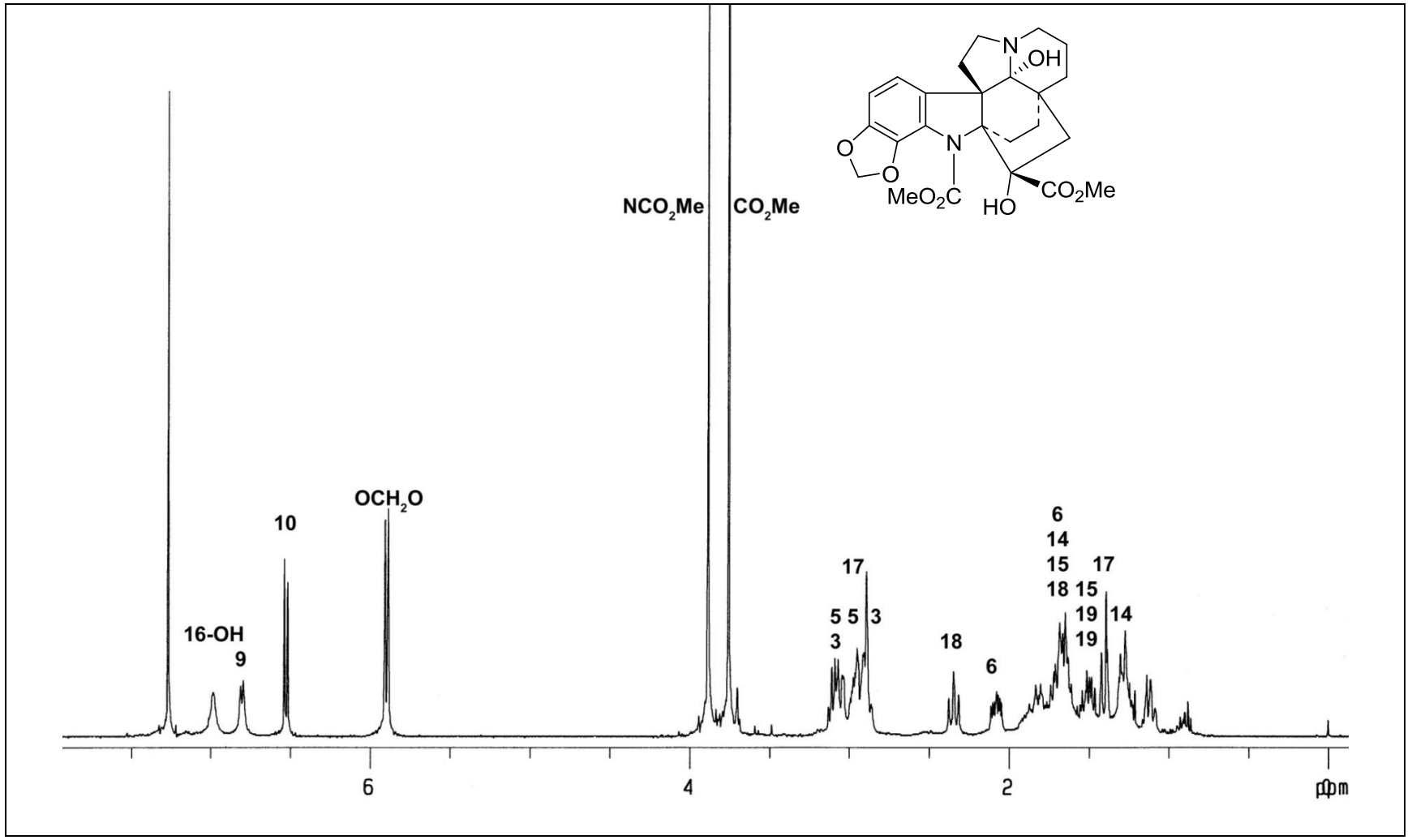


Figure 2.112: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of paucifinine (**83**)

2.2.6 Kopsine Alkaloids

2.2.6.1 Kopsanone (84), 11,12-Methylenedioxykopsine (85), 12-Methoxykopsine (86), Kopsifine (87), and *N*(1)-Decarbomethoxykopsifine (88)

Five known kopsine-type alkaloids were isolated, *viz.*, kopsanone (**84**),[211] 11,12-methylenedioxykopsine (**85**),[188] 12-methoxykopsine (**86**),[161] kopsifine (**87**),[188,190] and *N*(1)-decarbomethoxykopsifine (**88**).[188] The ^{1}H NMR spectra of these compounds are shown in Figures 2.113–2.117, while the NMR spectroscopic data of these compounds are summarized in Tables 2.57–2.59. Other data are given in the Experimental Section.

Table 2.57: ^{1}H and ^{13}C NMR Spectroscopic Data of Kopsanone (**84**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	69.5	14	1.80 m	
3	3.03 m	46.7	15	1.30 m	15.4
	3.03 m			1.30 m	
5	3.13 dd (10, 5)	54.3	16	2.69 br d (11)	52.3
	3.50 t (10)		17	1.62 ddd (14, 11, 1)	33.6
6	2.57 ddd (10, 5, 2)	57.3		2.03 d (14)	
7	–	63.1	18	1.30 m	33.9
8	–	133.1		1.51 dt (14, 3)	
9	7.30 br d (8)	122.8	19	1.30 m	36.3
10	6.79 td (8, 1)	119.6		1.30 m	
11	7.06 td (8, 1)	127.7	20	–	31.2
12	6.67 br d (8)	110.9	21	3.37 d (1)	70.5
13	–	150.8	22	–	218.2
14	1.80 m	24.2	NH	3.60 br s	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

Table 2.58: ^{1}H and ^{13}C NMR Spectroscopic Data of 11,12-Methylenedioxykopsine (**85**) and 12-Methoxykopsine (**86**)[a]

Position	**85**		**86**	
	δ_H	δ_C	δ_H	δ_C
2	–	75.3	–	76.6
3	3.01 m	46.4	3.03 m	46.4
	3.01 m		3.03 m	
5	3.13 dd (10, 5)	53.8	3.16 m	53.8
	3.51 t (10)		3.58 m	
6	2.57 dd (10, 5)	53.5	2.70 dd (10, 5)	52.3
7	–	59.7	–	61.0
8	–	131.8	–	138.0
9	7.04 d (8)	115.4	7.08 d (8)	115.0
10	6.32 d (8)	105.1	7.14 t (8)	127.1
11	–	149.0	6.68 dd (8, 1)	112.2
12	–	135.7	–	150.5
13	–	123.9	–	130.7
14	1.26 m	15.3	1.30 m	15.4
	1.79 m		1.80 m	
15	1.34 m	33.2	1.27 m	34.9
	1.34 m		1.51 m	
16	–	82.2	–	82.0
17	1.58 br d (15)	44.0	1.59 m	43.4
	2.39 dd (15, 3)		2.38 dd (15, 4)	
18	1.68 ddd (14, 12, 5)	19.6	1.66 ddd (14, 12, 5)	20.4
	2.51 ddd (14, 12, 4)		2.46 ddd (14, 12, 5)	
19	1.34 m	32.3	1.34 m	33.0
	1.56 m		1.55 m	
20	–	34.9	–	31.9
21	3.02 d (2)	69.6	3.18 s	69.2
22	–	214.0	–	214.2
NCO_2*Me*	3.81 s	53.6	3.73 s	55.9
N*C*O_2Me	–	155.6	–	156.4
OCH_2O	5.90 d (1.5)	100.5	–	–
	5.93 d (1.5)			
16-OH	7.09 s	–	7.00 s	–
12-OMe	–	–	3.83 s	53.6

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC and HMBC.

Table 2.59: ^{1}H and ^{13}C NMR Spectroscopic Data of Kopsifine (**87**) and *N*(1)-Decarbomethoxykopsifine (**88**)[a]

Position	**87**		**88**	
	δ_H	δ_C	δ_H	δ_C
2	–	74.9	–	71.9
3	2.91 td (13, 4)	40.7	2.91 td (13, 4)	40.8
	4.22 dd (13, 5)		4.23 dd (13, 5)	
5	–	164.3	–	164.7
6	2.91 s	59.0	2.92 s	59.6
7	–	52.6	–	53.6
8	–	128.6	–	127.1
9	6.72 d (8)	115.1	6.67 d (8)	115.2
10	6.63 d (8)	105.2	6.35 d (8)	100.5
11	–	149.9	–	148.9
12	–	136.1	–	132.6
13	–	123.9	–	132.4
14	1.51 m	19.3	1.53 m	19.5
	1.65 m		1.63 m	
15	1.46 m	32.6	1.46 m	33.0
	1.65 m		1.63 m	
16	–	83.1	–	82.3
17	1.61 br d (15)	39.3	1.50 br d (15)	37.6
	2.13 dd (15, 3)		1.99 dd (15, 3)	
18	1.70 m	18.8	1.75 m	20.1
	2.56 ddd (13.5, 12, 4.5)		2.09 td (13, 4.5)	
19	1.43 m	31.8	1.43 m	32.8
	1.80 td (12, 4.5)		1.73 m	
20	–	32.8	–	34.7
21	3.62 d (2)	65.4	3.66 br s	65.6
22	–	202.5	–	204.6
NCO_2*Me*	3.82 s	53.8	–	–
N*C*O_2Me	–	155.3	–	–
OCH_2O	5.94 d (1.5)	100.9	5.86 d (1.5)	101.1
	5.96 d (1.5)		5.91 d (1.5)	
16-OH	7.09 br s	–	–	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

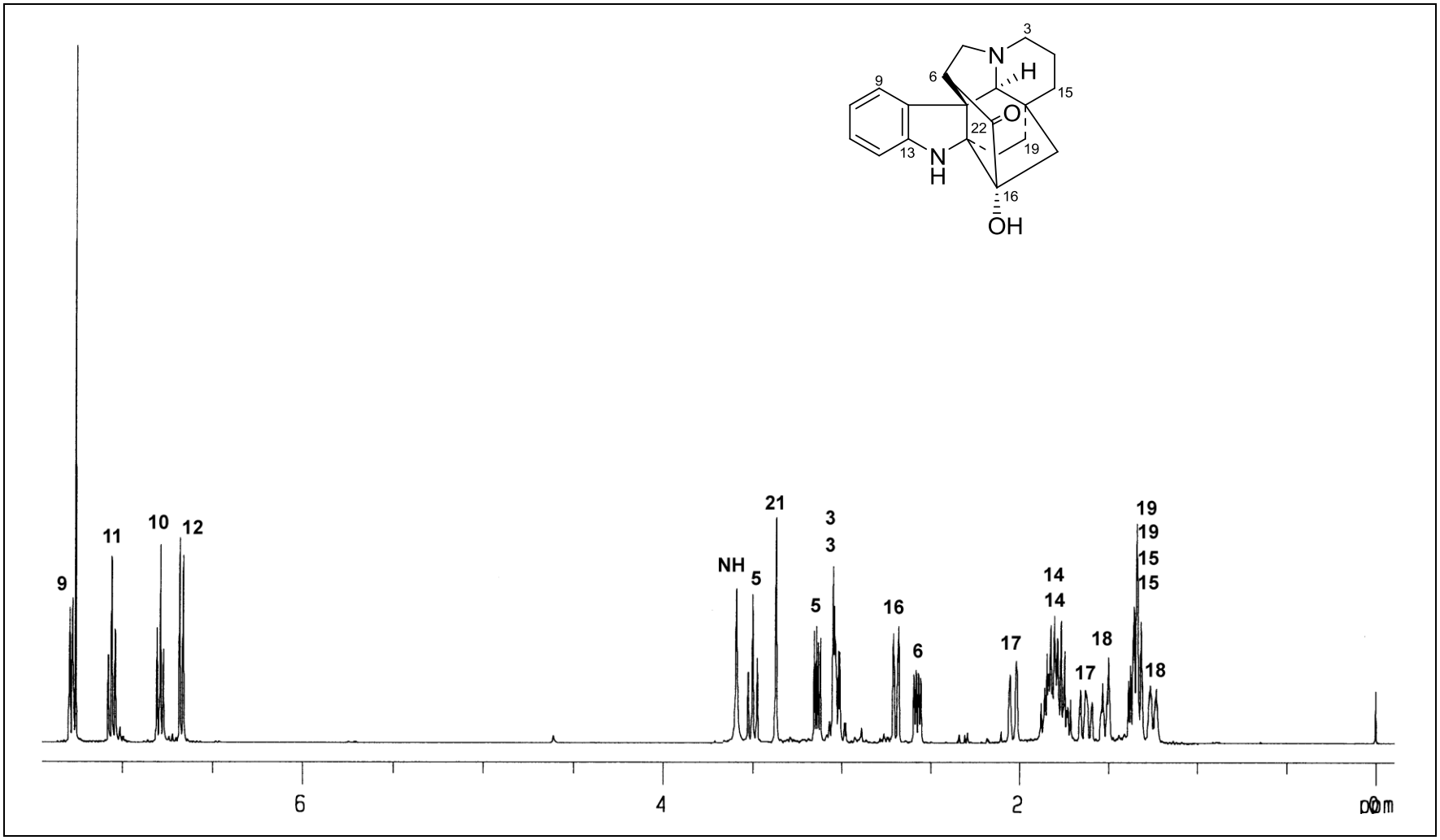


Figure 2.113: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of kopsanone (**84**)

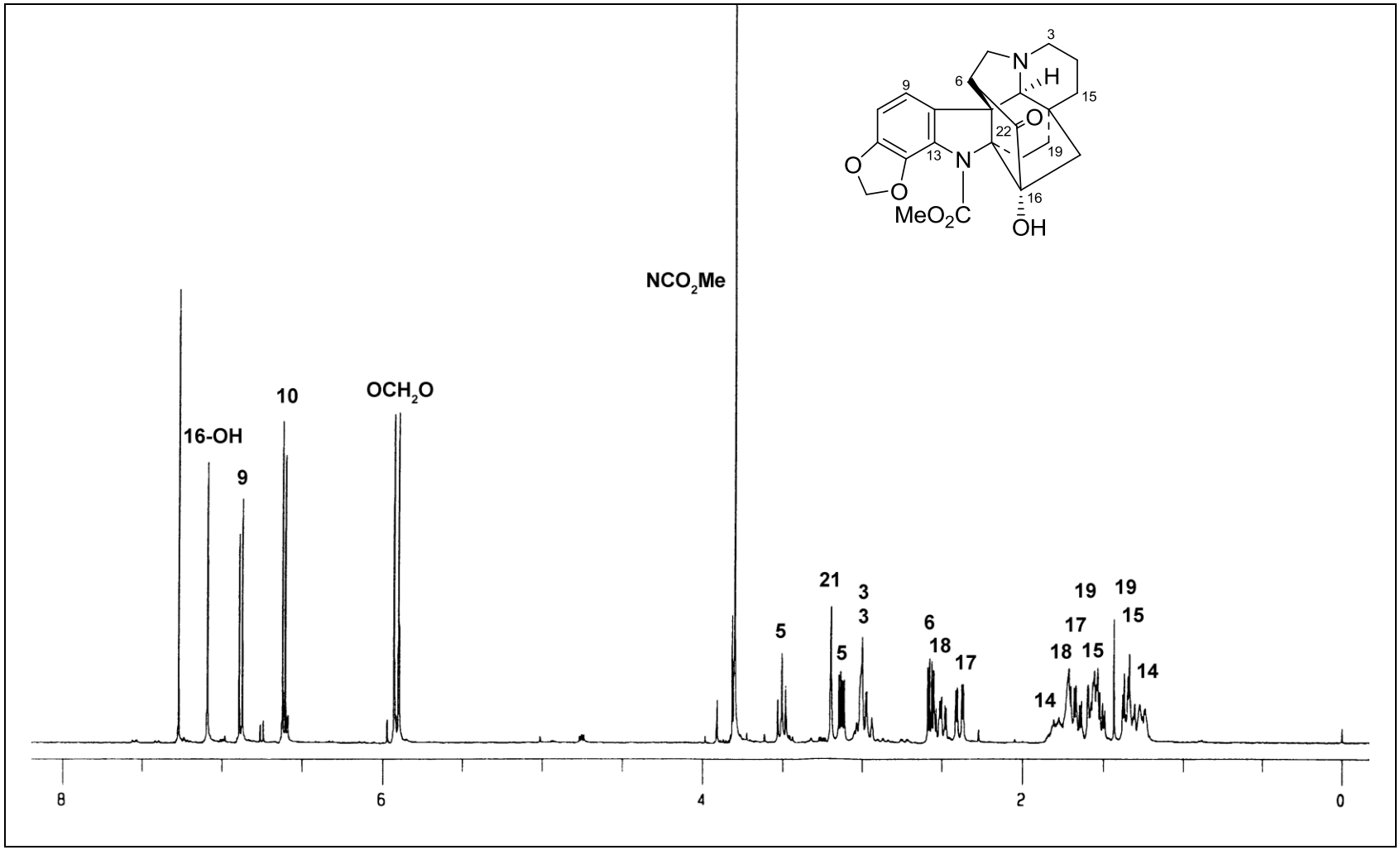


Figure 2.114: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 11,12-methylenedioxykopsine (**85**)

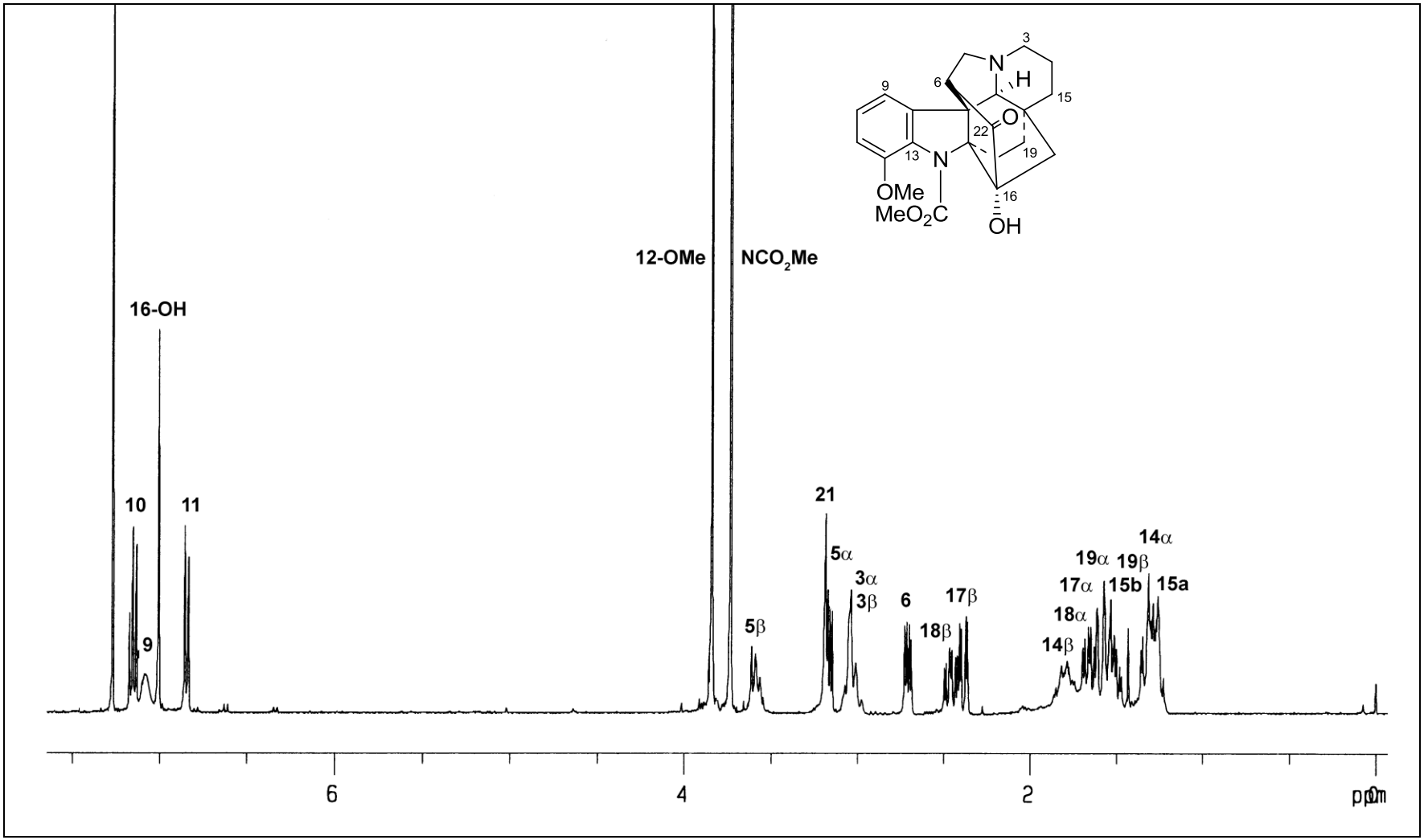


Figure 2.115: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 12-methoxykopsine (**86**)

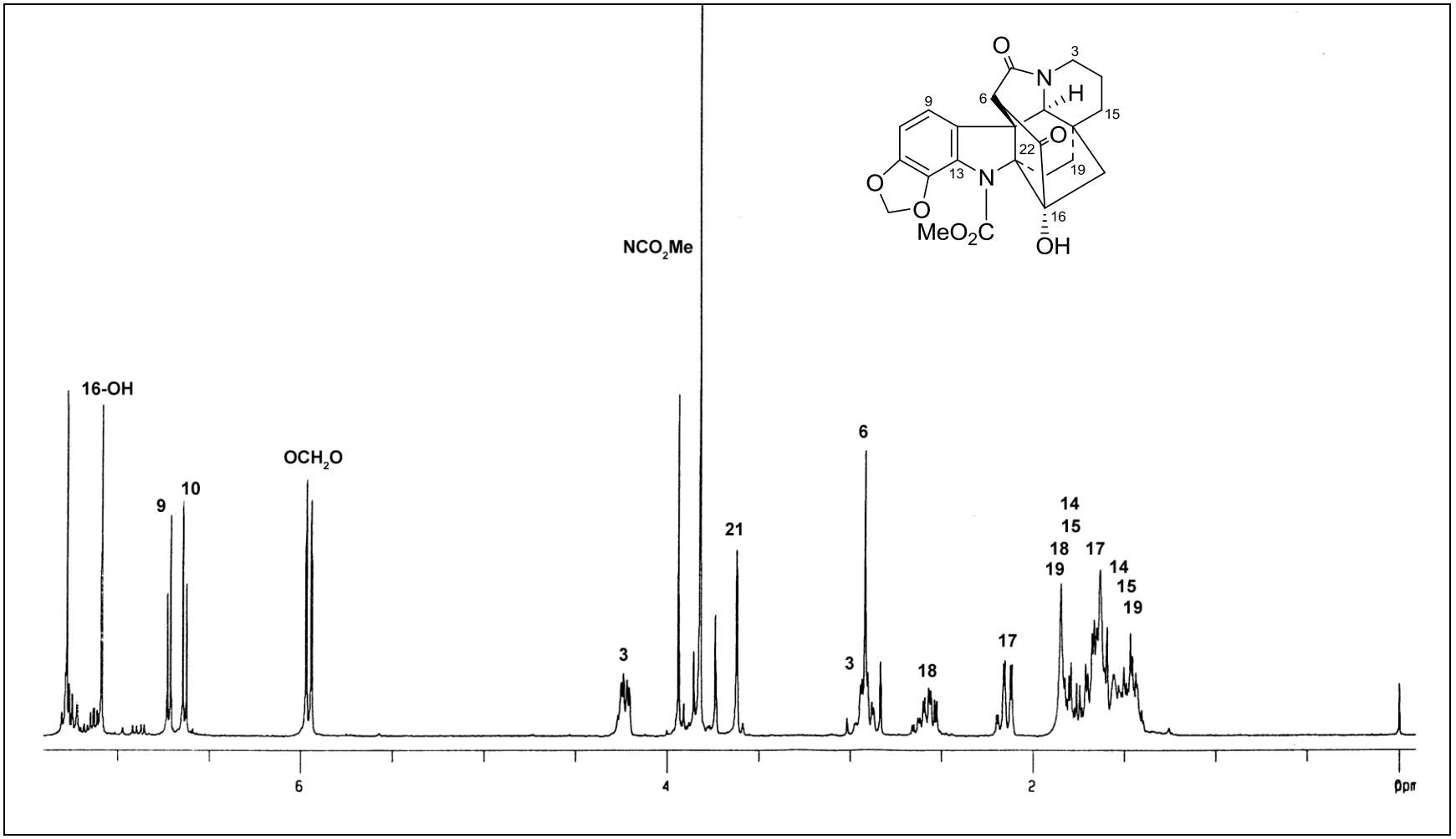


Figure 2.116: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of kopsifine (**87**)

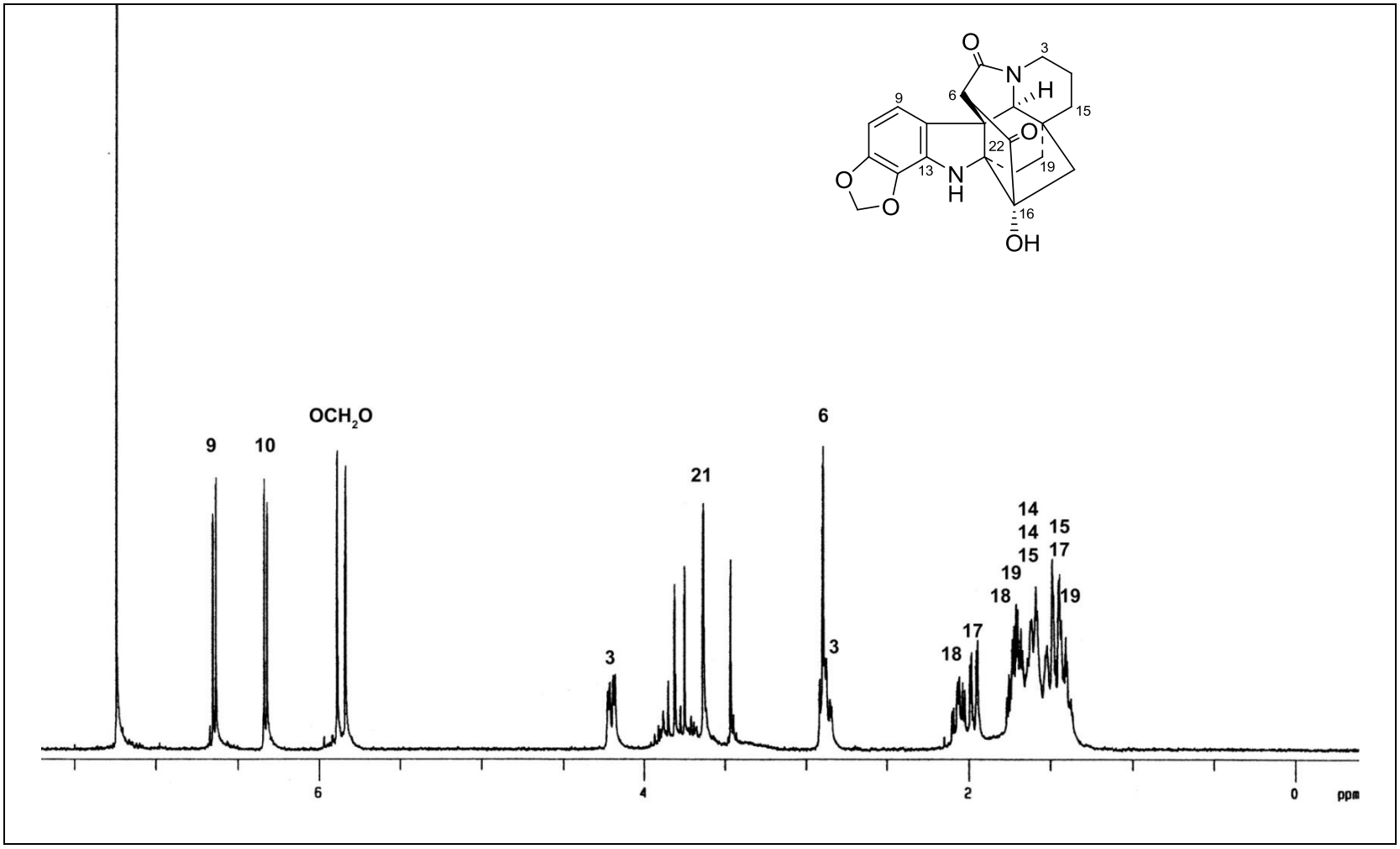


Figure 2.117: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *N*(1)-decarbomethoxykopsifine (**88**)

2.2.7 *Strychnos* Alkaloids

2.2.7.1 Akuammicine (89)

The only known *Strychnos*-type alkaloid isolated from *K. pauciflora* is akuammicine (**89**).[376,377] The ^{1}H NMR spectrum of this compound is shown in Figure 2.118, while the complete assignments of the NMR spectroscopic data of this compound are summarized in Table 2.60. Other data are given in the Experimental Section.

Table 2.60: ^{1}H and ^{13}C NMR Spectroscopic Data of Akuammicine (**89**)[a]

Position	δ_H	δ_C
2	–	167.1
3	4.25 br s	61.7
5	3.11 dd (13, 7)	55.7
	3.46 td (13, 6)	
6	1.93 dd (13, 6)	45.6
	2.56 td (13, 7)	
7	–	57.0
8	–	136.2
9	7.30 br d (8)	120.9
10	6.92 td (8, 1)	121.1
11	7.18 td (8, 1)	128.0
12	6.84 br d (8)	109.5
13	–	143.3
14	1.36 dt (14, 3)	29.5
	2.50 ddd (14, 3, 2)	
15	4.03 m	30.5
16	–	101.4
18	1.63 d (7)	13.0
19	5.46 br q (7)	122.4
20	–	137.5
21	3.08 d (14)	56.5
	4.03 m	
NH	9.00 br s	–
CO_2*Me*	3.82 s	51.1
CO_2Me	–	167.7

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

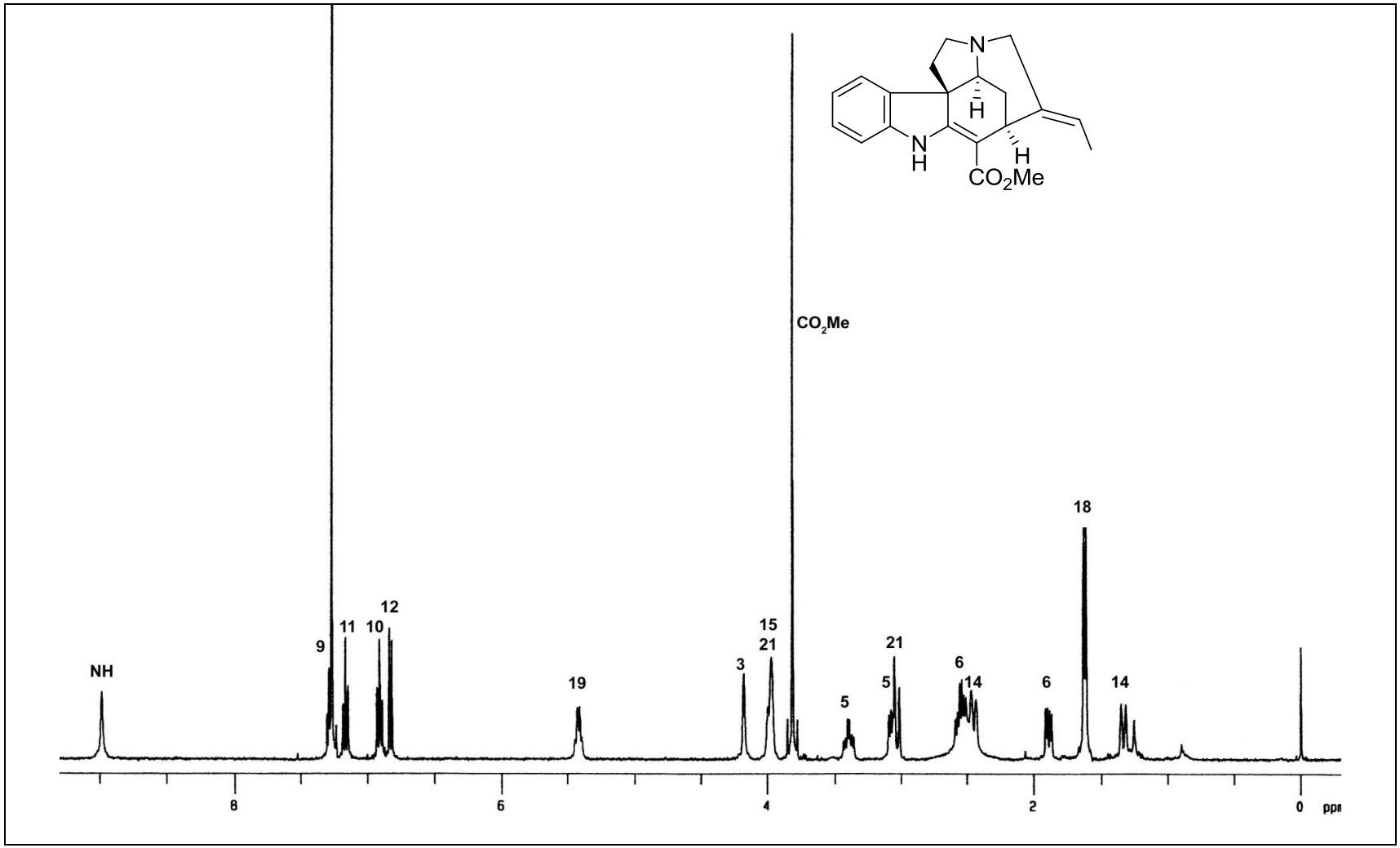
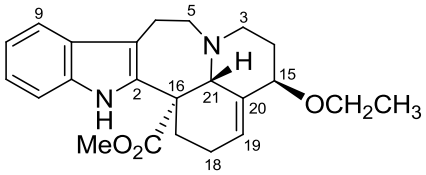


Figure 2.118: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of akuammicine (**89**)

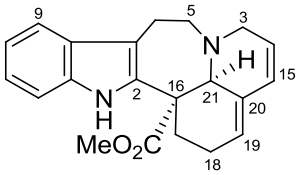
2.2.8 Aspidospermatan Alkaloids

2.2.8.1 Andransinine (90)

Andransinine (**90**) was obtained as an optically inactive alkaloid (light yellowish oil, $[\alpha]_D$ 0 ($CHCl_3$, *c* 0.15)) It was subsequently obtained as light yellow crystals from CH_2Cl_2/hexanes, mp 186–190 ^oC. The UV spectrum of **90** was characteristic of an indole chromophore with absorption maxima at 224 and 283 nm, while the IR spectrum indicated the presence of NH (3391 cm^{-1}), Wenkert-Bohlmann bands (2885 and 2840 cm^{-1}), and ester carbonyl (1727 cm^{-1}) functions. The ESIMS of **90** showed an $[M + H]^+$ peak at *m*/*z* 381 and the HRESIMS measurements yielded the molecular formula as $C_{23}H_{28}N_2O_3$ (DBE 11).



90



474

The ^1H NMR spectrum (Figure 2.120) of **90** showed the presence of an unsubstituted indole moiety from the presence of four aromatic resonances (δ 7.51, br d, *J* = 7.7 Hz, H(9); 7.11, td, *J* = 7.7, 1 Hz, H(10); 7.17, td, *J* = 7.7, 1 Hz, H(11); 7.33, br d, *J* = 7.7 Hz, H(12)), an indolic NH as a broad singlet at δ 8.21, an isolated aminomethine at δ 3.79, a methoxy group associated with a methyl ester function at δ 3.63, a vinylic hydrogen at δ 5.74, and an ethoxy group. The ^{13}C NMR data of **90** (Table 2.61) indicated the presence

of 23 carbon resonances, comprising two methyl, seven methylene, seven methine, and seven quaternary carbon atoms, in agreement with the molecular formula.

Detailed examination of the ^{1}H and ^{13}C NMR data (Table 2.61) of **90** revealed that the structure of compound **90** is identical to that of andransinine reported earlier (the small optical rotation observed previously was likely a result of racemate contamination).[313,378] The structure was also confirmed by an X-ray diffraction analysis (crystals from CH_2Cl_2/hexanes) as shown in Figure 2.119, which also revealed the presence of a pair of enantiomers in the crystal lattice.

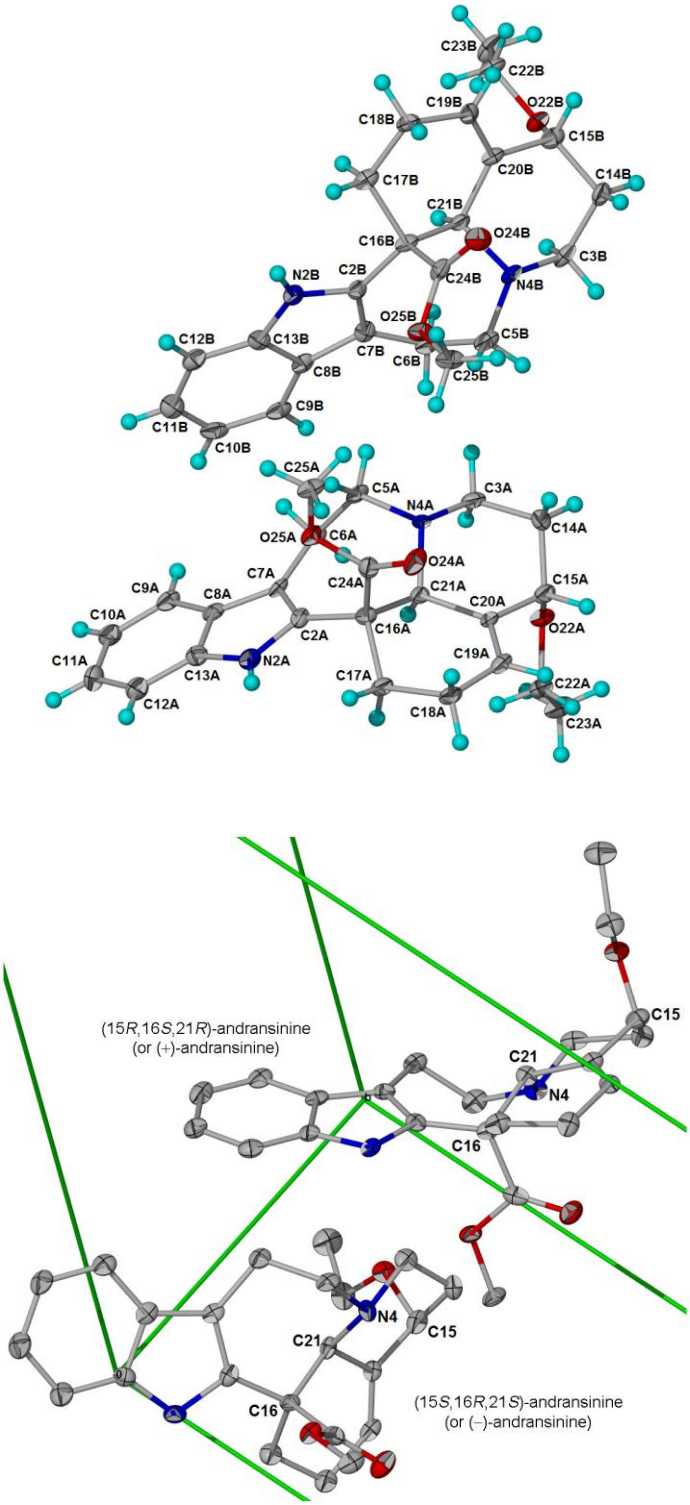


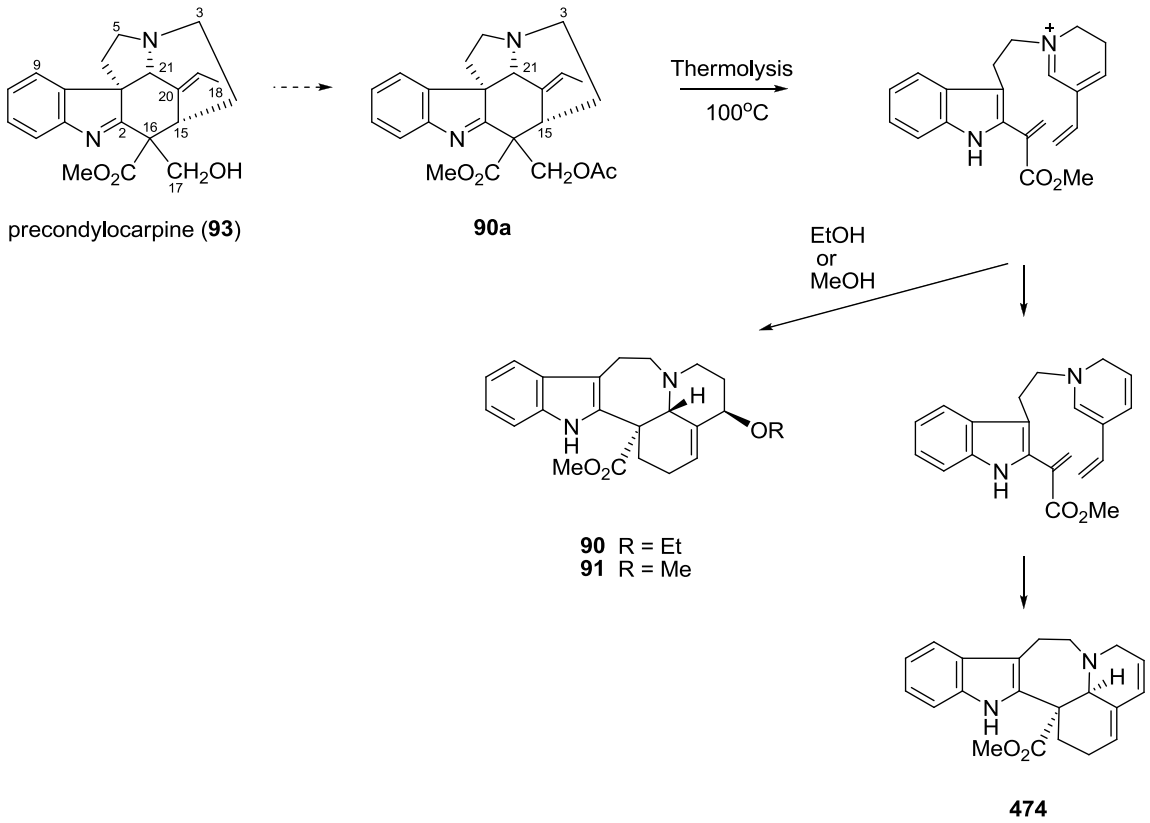
Figure 2.119: Top: X-ray crystal structure of **90**; Bottom: Partial unit cell for crystals of **90**, obtained from CH_2Cl_2/hexanes solution. It can be seen that (±)-andransinine are present in the unit cell.

2.2.8.2 Compound 91

Compound **91** was also isolated as a racemate (light yellowish oil, $[\alpha]_D$ 0 ($CHCl_3$, *c* 0.03)). The UV and IR spectra were similar to those of andransinine (**90**), suggesting an andranginine-type compound with similar functionalities. The ESIMS of **91** showed an $[M + H]^+$ peak at *m*/*z* 367 and HRESIMS measurements yielded the molecular formula $C_{22}H_{26}N_2O_3$, 14 mass units lower than that of **90**. The ^1H and ^{13}C NMR data (Table 2.61) of **91** were very similar to those of **90**, except for the absence of the ethoxy side chain and the presence instead of an OMe group in the ^1H NMR spectrum of **91**. The OMe substituent was readily deduced to be at C(15) since the chemical shifts of the other carbons were essentially unchanged. The COSY and HSQC data revealed partial structures that are similar to those of compound **90**, providing additional support for the placement of the methoxy function at C(15). This was also supported by the observed three-bond correlation from the 15-OMe to C(15) in the HMBC spectrum. The relative configurations at the various stereogenic centers were deduced to be similar to compound **90** by examination of the NMR data as well as the NOE experiments. Compound **91** is therefore the C(15) methoxy analogue of andransinine (**90**).

The lack of optical activity in **90** and **91** suggested that these compounds are in all probability artifacts formed during the isolation process. A non-enzymatic pathway (involving a 4 + 2 cycloaddition as the key step) was presented to account for the isolation of racemic andranginine (**474**) from *Craspidospermum verticillatum* which was supported by the observation that thermolysis of the putative precursor, precondylocarpine acetate (**90a**), at 100 ^oC in EtOAc solution, resulted in the formation

of racemic andranginine (**474**), while carrying out the thermolysis in MeOH led to the formation of methoxyandranginine (Scheme 2.10).[379] It is therefore likely that both ethoxyandranginine (**90**) and methoxyandranginine (**91**) are artifacts, formed by a similar pathway (Scheme 2.10) since compound **93** was present among the alkaloids isolated and denatured ethanol was used in the extraction of the plant materials.



Scheme 2.10: Formation of **90** and **91** from a precondylocarpine precursor[379]

Table 2.61: ^{1}H and ^{13}C NMR Spectroscopic Data of Andransinine (**90**) and Compound **91**[a]

Position	**90**		**91**	
	δ_H	δ_C	δ_H	δ_C
2	–	138.0	–	137.8
3	2.74 m	50.0	2.72 m	49.8
	3.23 m		3.18 m	
5	3.15 m	57.0	3.17 m	56.9
	3.33 m		3.33 dd (14.5, 10.6)	
6	2.79 dd (16, 5.7)	18.6	2.78 dd (16.8, 5.5)	18.5
	3.08 m		3.08 dd (16.8, 10.6)	
7	–	114.8	–	114.9
8	–	127.7	–	127.6
9	7.51 br d (7.7)	118.4	7.49 br d (7.7)	118.4
10	7.11 td (7.7, 1)	119.5	7.10 td (7.7, 1)	119.5
11	7.17 td (7.7, 1)	121.9	7.18 td (7.7, 1)	121.9
12	7.33 br d (7.7)	110.8	7.33 br d (7.7)	110.7
13	–	134.9	–	134.8
14	1.95 br dd (13.6, 2.7)	32.4	1.96 br dd (13.6, 2.7)	32.4
	2.07 m		2.10 m	
15	3.80 m	78.1	3.66 m	80.0
16	–	48.6	–	48.5
17	2.07 m	32.3	2.10 m	32.1
	2.49 dd (12.7, 2.7)		2.51 br d (12)	
18	2.16 m	22.2	2.22 m	22.2
	2.28 m		2.27 m	
19	5.74 d (5.4)	126.0	5.77 d (5.4)	126.7
20	–	134.1	–	133.3
21	3.79 s	63.5	3.76 s	63.3
22	3.19 m	62.2	–	–
	3.37 m			
23	1.12 t (7)	15.4	–	–
NH	8.21 s	–	8.17 br s	–
15-OMe	–	–	3.63 s	54.8
CO_2*Me*	3.63 s	52.3	3.12 s	52.4
CO_2Me	–	171.8	–	171.8

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY/DNOE.

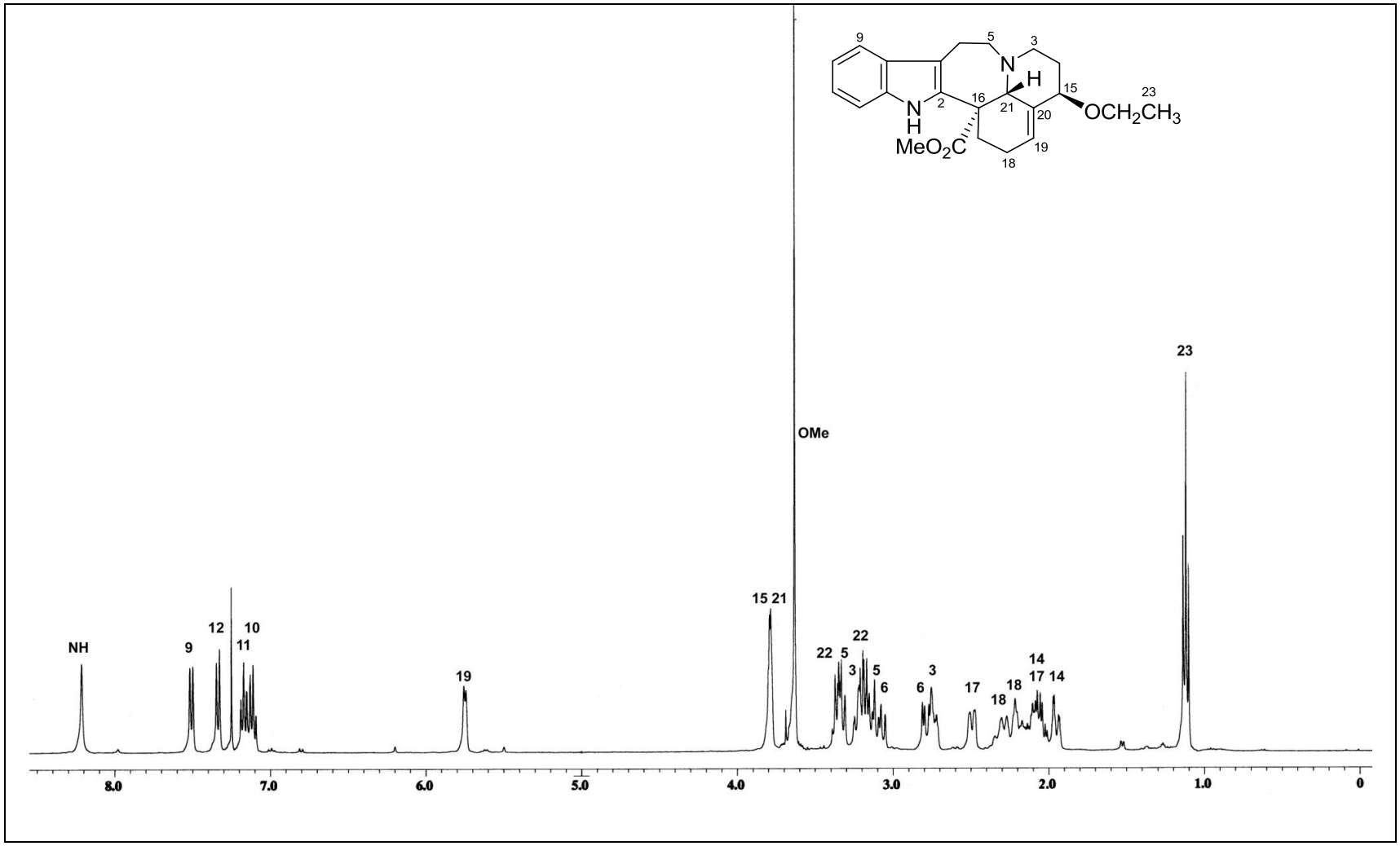


Figure 2.120: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of andransinine (**90**)

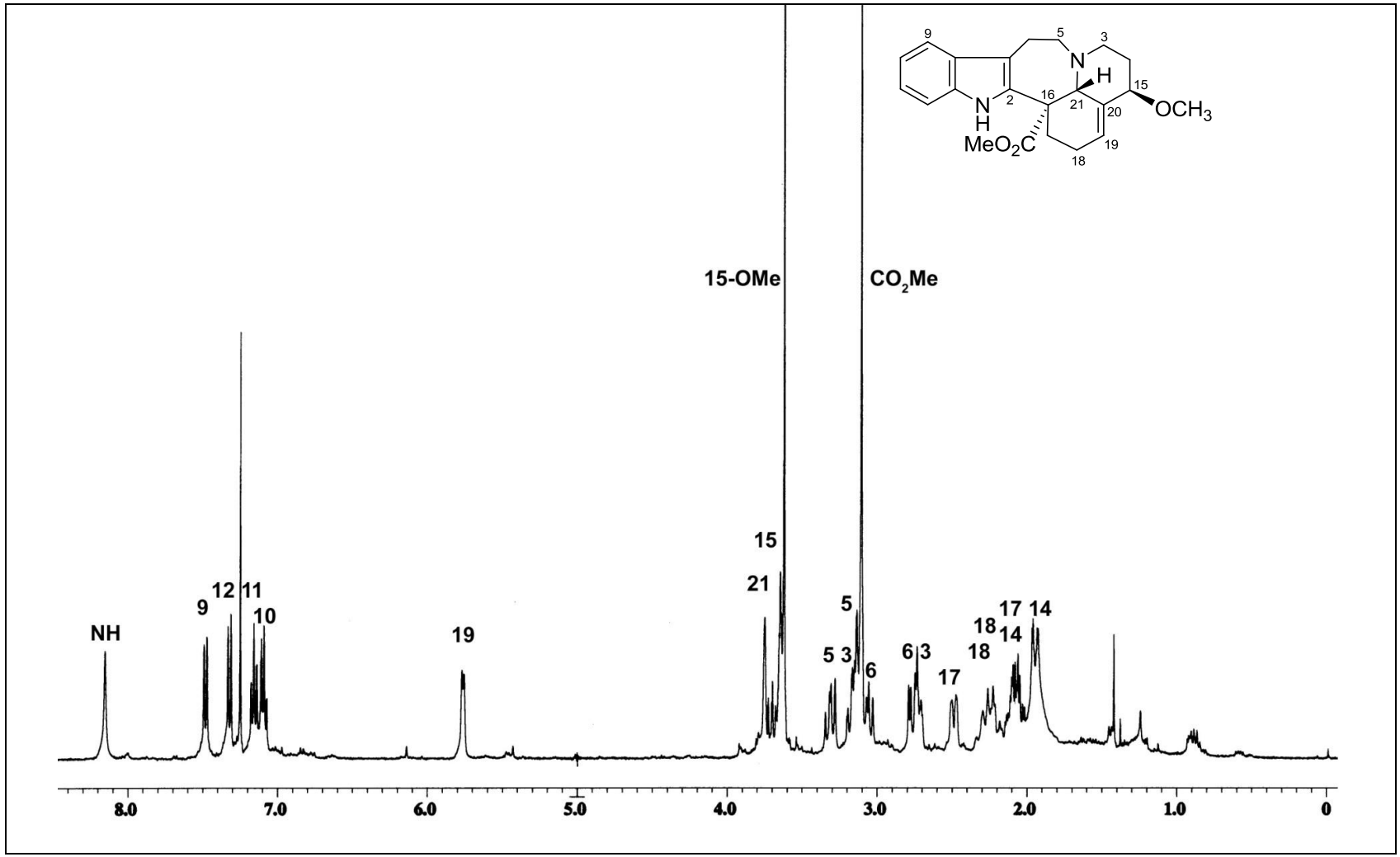


Figure 2.121: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of compound **91**

2.2.8.3 Condylocarpine (92), Precondylocarpine (93), and Stemmadenine (94)

The known condylocarpine-type alkaloids isolated from *K. pauciflora* are condylocarpine (**92**),[380,381] precondylocarpine (**93**),[381,382] and stemmadenine (**94**).[383,384] The ^{1}H NMR spectra of these compounds are shown in Figures 2.122–2.124. The ^{1}H and ^{13}C NMR spectroscopic data are summarized in Tables 2.62 and 2.63. Other data are given in the Experimental Section.

Table 2.62: ^{1}H and ^{13}C NMR Spectroscopic Data of Condylocarpine (**92**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	169.2	13	–	144.4
3	2.66 ddd (12.9, 7.6, 5.4)	45.9	14	1.88 m	28.2
	3.03 ddd (12.9, 7.3, 5.6)			1.88 m	
5	2.97 ddd (11.5, 6.8, 3.4)	52.9	15	3.91 ddd (6.6, 3.4, 2)	28.9
	3.09 ddd (11.5, 9.8, 6.8)		16	–	101.4
6	1.97 ddd (12.9, 6.8, 3.4)	45.0	18	1.59 d (6.8)	13.0
	2.77 ddd (12.9, 9.5, 6.8)		19	5.32 q (6.8)	117.4
7	–	59.8	20	–	137.2
8	–	135.2	21	4.13 br d (1.7)	68.7
9	7.17 br d (7)	120.1	NH	8.67 br s	–
10	6.89 td (7, 1)	121.0	CO_2*Me*	3.79 s	51.2
11	7.11 td (7, 1)	127.6	*C*O_2Me	–	168.0
12	6.78 br d (7)	109.6			

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

Table 2.63: ^{1}H and ^{13}C NMR Spectroscopic Data of Precondylocarpine (**93**) and Stemmadenine (**94**)[a]

Position	**93**		**94**	
	δ_H	δ_C	δ_H	δ_C
2	–	187.5	–	133.2
3	2.68 dt (14, 4.6)	48.1	2.67 dd (14.5, 6.3)	45.5
	3.08 m		2.84 m	
5	3.31 dd (12, 7.4)	58.2	3.03 m	55.9
	3.51 td (12, 6.3)		3.03 m	
6	1.98 dd (14, 6.3)	38.9	3.01 m	27.2
	3.03 m		3.17ddd (14.5, 10, 4)	
7	–	68.6	–	113.6
8	–	146.0	–	127.9
9	7.37 d (7.2)	120.6	7.42 br d (7.7)	118.0
10	7.24 t (7.2)	126.7	6.99 td (7.7, 1)	119.0
11	7.31 t (7.2)	127.8	7.04 td (7.7, 1)	121.6
12	7.50 d (7.2)	120.6	7.22 br d (7.7)	111.1
13	–	152.5	–	135.3
14	2.08 m	30.3	1.96 ddd (14.5, 12, 5.4)	29.0
	2.08 m		2.27 m	
15	3.03 m	34.5	3.47 dd (12, 3)	37.7
16	–	61.9	–	61.1
17	3.90 d (10.5)	70.9	4.16 d (10.4)	69.6
	3.90 d (10.5)		4.27 d (10.4)	
18	1.56 d (7)	13.3	1.57 dd (7, 2.3)	14.2
19	5.39 q (7)	123.8	5.25 q (7)	124.3
20	–	133.1	–	134.4
21	4.03 d (1.8)	75.0	2.80 m	55.4
			3.08 m	
OH	5.56 br s	–	–	–
NH	–	–	9.44 br s	–
CO_2*Me*	3.84 s	52.6	3.67 s	52.4
CO_2Me	–	172.9	–	174.1

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

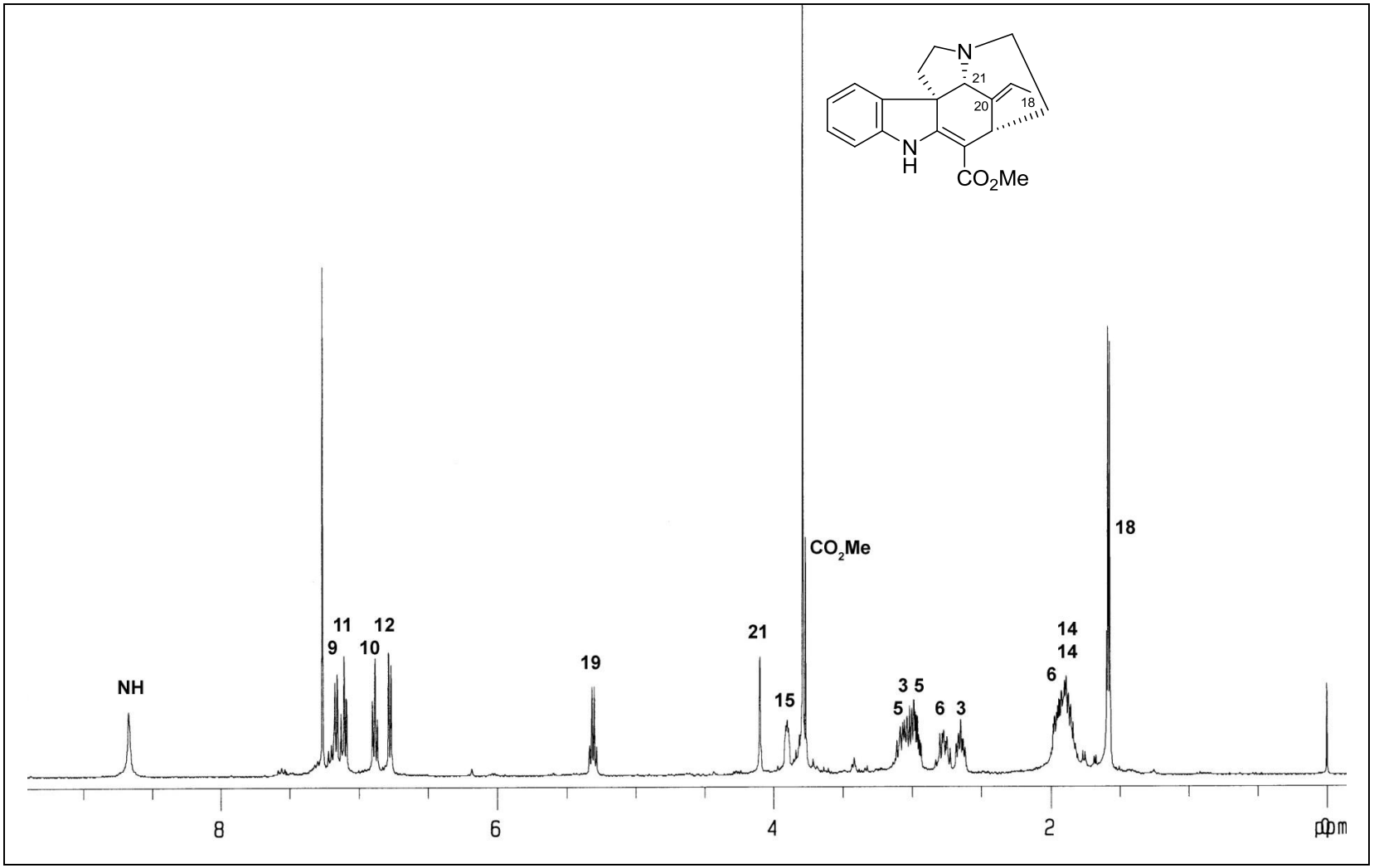


Figure 2.122: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of condylocarpine (**92**)

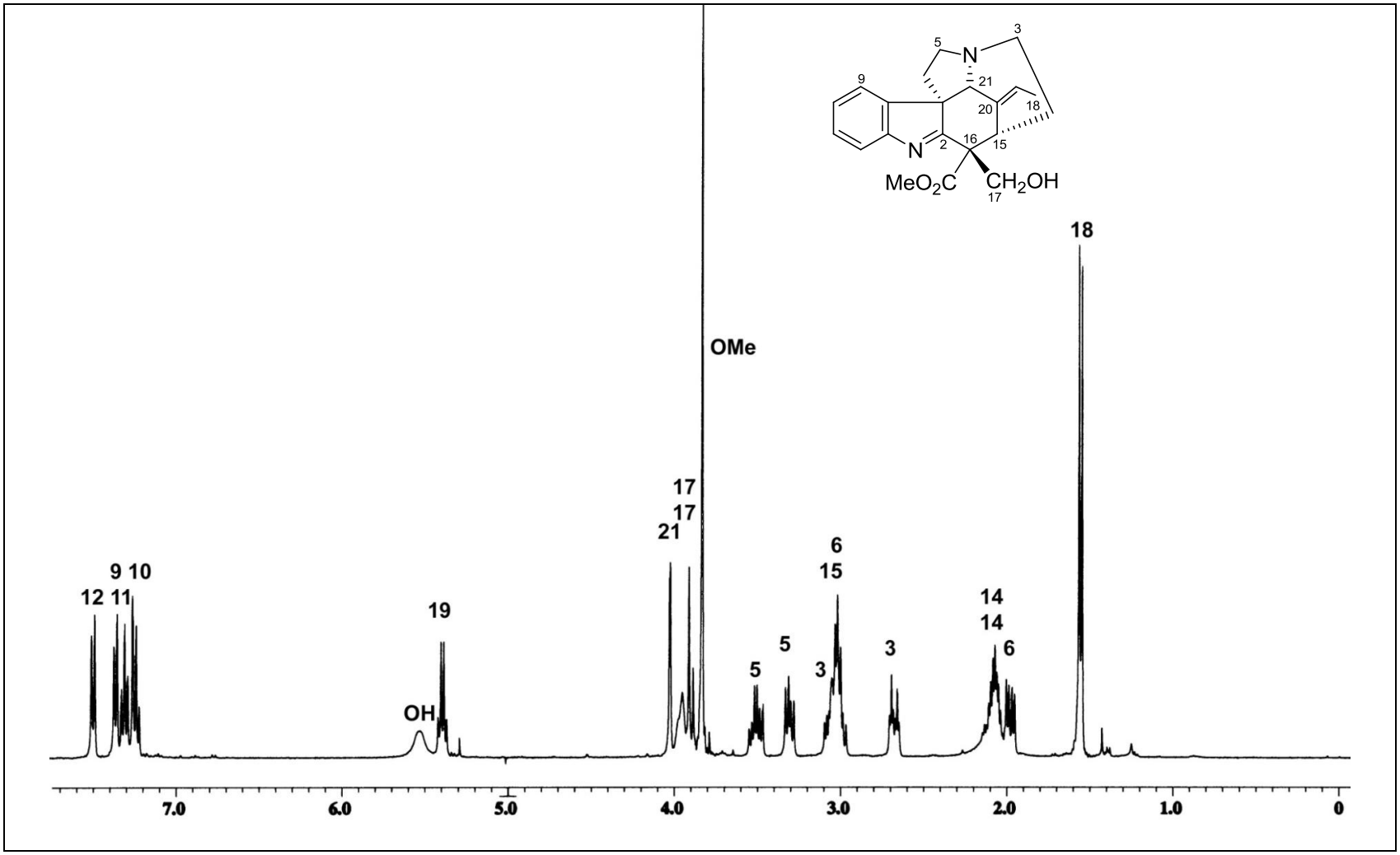


Figure 2.123: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of precondylocarpine (**93**)

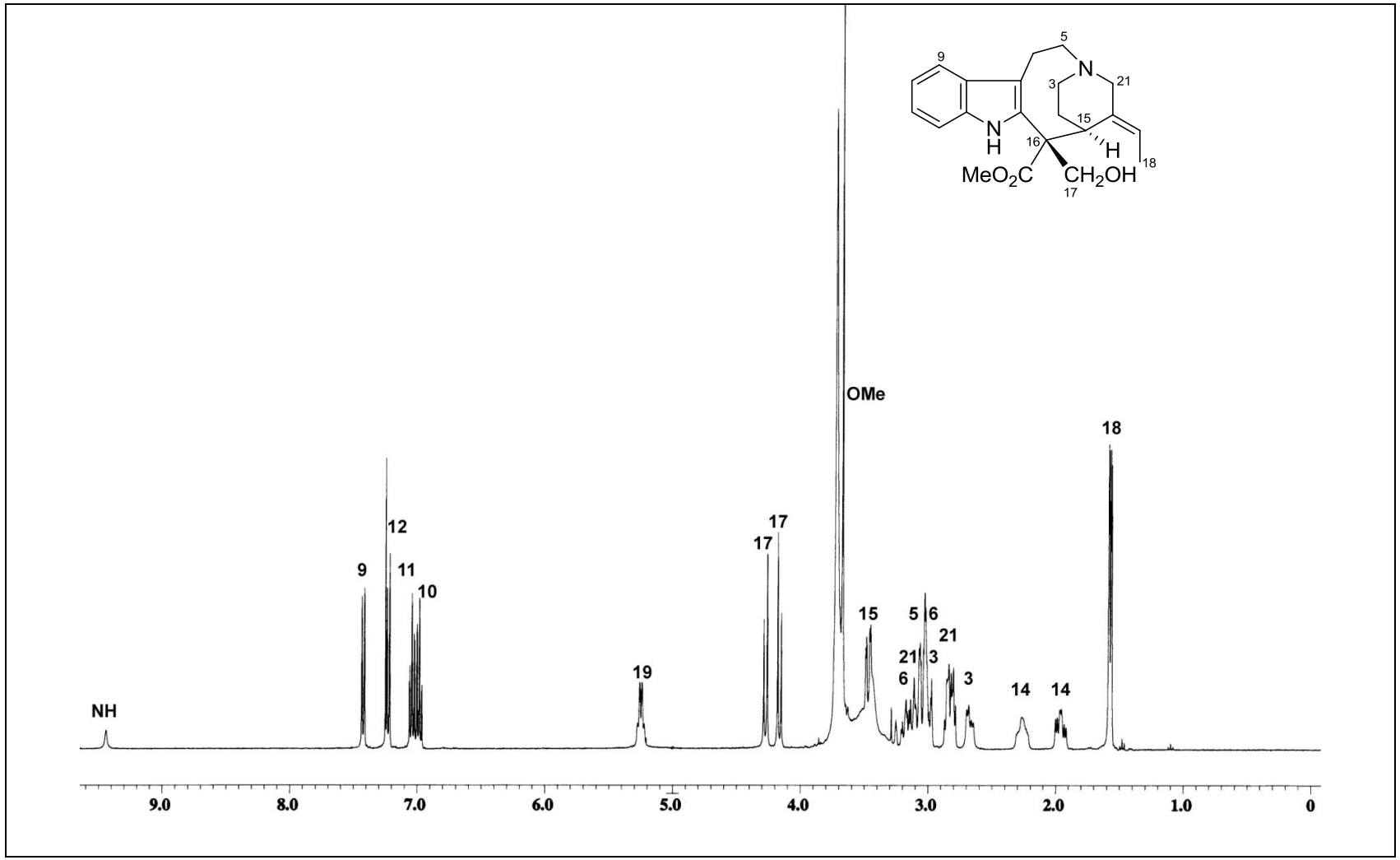


Figure 2.124: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of stemmadenine (**94**)

2.2.9 Methyl chanofruticosinate Alkaloids

2.2.9.1 Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (95), Methyl 11,12-methylenedioxychanofruticosinate (96), Methyl chanofruticosinate (97), Methyl *N*(1)-decarbomethoxychanofruticosinate (98), and Methyl 12-methoxychanofruticosinate (99)

Five known methyl chanofruticosinate alkaloids, *viz.*, methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (**95**),[152] methyl 11,12-methylenedioxychanofruticosinate (**96**),[175] methyl chanofruticosinate (**97**),[175] methyl *N*(1)-decarbomethoxychanofruticosinate (**98**),[175] and methyl 12-methoxychanofruticosinate (**99**)[163] were also obtained from *K. pauciflora* in the present study. The ^{1}H NMR spectra of these compounds (**95**–**99**) are shown in Figures 2.125–2.129, while the complete assignments of the NMR spectroscopic data of compounds **95**–**99** are summarized in Tables 2.64–2.66. Other data are given in the Experimental Section.

Table 2.64: ^{1}H and ^{13}C NMR Spectroscopic Data of Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (**95**) and Methyl 11,12-methylenedioxychanofruticosinate (**96**)[a]

Position	**95**		**96**	
	δ_H	δ_C	δ_H	δ_C
2	–	74.6	–	76.5
3	2.92 m	46.6	3.03 m	46.3
	2.92 m		3.03 m	
5	2.98 m	52.6	2.92 d (11)	52.2
	3.71 dd (11, 6)		3.75 dd (11, 6)	
6	3.26 d (6)	55.3	3.02 d (6)	55.3
7	–	57.6	–	58.2
8	–	130.0	–	128.9
9	6.62 d (8)	116.6	6.80 d (8)	116.7
10	6.34 d (8)	100.3	6.57 d (8)	103.1
11	–	148.1	–	148.8
12	–	129.4	–	123.9
13	–	131.6	–	133.7
14	1.30 m	17.4	1.40 m	17.3
	1.87 m		1.96 m	
15	1.30 m	34.9	1.46 m	35.5
	1.87 m		1.46 m	
16	–	209.2	–	207.5
17	2.02 d (19)	42.6	2.15 d (19)	43.0
	2.83 d (19)		2.89 d (19)	
18	1.80 m	27.6	2.27 dd (16, 8)	23.3
	1.92 m		3.00 m	
19	1.30 m	34.6	1.40 m	34.6
	1.53 br d (13)		1.64 br d (14)	
20	–	36.3	–	35.8
21	2.49 s	68.3	2.53 s	68.3
CO_2*Me*	3.64 s	52.3	3.66 s	52.4
CO_2Me	–	174.7	–	170.7
NCO_2*Me*	–	–	3.89 s	52.7
N*C*O_2Me	–	–	–	152.8
OCH_2O	5.89 d (1.5)	101.0	6.00 m	100.5
	5.93 d (1.5)		6.00 m	
NH	4.47 br s	–	–	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

Table 2.65: ^{1}H NMR Spectroscopic Data of Methyl chanofruticosinate (**97**), Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**), and Methyl 12-methoxy-chanofruticosinate (**99**)[a]

H	**97**	**98**	**99**
3	2.99 m	2.95 m	2.98 m
	2.99 m	2.95 m	2.98 m
5	2.81 d (11)	2.95 m	2.95 m
	3.71 dd (11, 6)	3.76 dd (11, 6)	3.80 m
6	2.84 d (6)	3.31 d (6)	3.22 d (6)
9	7.31 d (7)	7.11 d (7)	6.88 d (8)
10	7.00 t (7)	6.79 t (7)	7.05 t (8)
11	7.13 t (7)	7.09 t (7)	6.84 d (8)
12	7.74 d (7)	6.76 d (7)	–
14	1.32 m	1.28 m	1.40 m
	1.85 m	1.85 m	1.94 m
15	1.56 m	1.28 m	1.37 m
	1.56 m	1.85 m	1.57 m
17	2.16 d (19)	2.04 d (19)	2.07 d (19)
	2.77 d (19)	2.84 d (19)	2.90 d (19)
18	2.50 m	1.70 m	1.98 m
	2.67 m	1.90 m	3.29 dt (17, 4)
19	1.32 m	1.28 m	1.36 m
	1.56 m	1.54 br d (13)	1.36 m
21	2.48 s	2.50 s	2.51 s
NH	–	4.48 br s	–
CO_2Me	3.58 s	3.61 s	3.57 s
NCO_2Me	3.86 s	–	3.82 s
12-OMe	–	–	3.85 s

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

Table 2.66: ^{13}C NMR Spectroscopic Data of Methyl chanofruticosinate (**97**), Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**), and Methyl 12-methoxy-chanofruticosinate (**99**)[a]

C	**97**	**98**	**99**
2	73.9	73.8	77.2
3	46.3	46.5	46.3
5	52.3	52.6	52.5
6	56.2	55.1	54.6
7	57.7	57.6	59.9
8	132.8	133.1	130.0
9	124.7	123.9	116.1
10	122.9	119.8	124.9
11	128.4	128.0	112.3
12	114.2	110.1	148.6
13	141.2	147.7	138.0
14	17.3	17.4	17.4
15	35.6	34.9	34.4
16	207.9	209.3	208.5
17	43.3	42.5	43.2
18	24.3	27.4	23.4
19	35.3	34.6	35.7
20	34.8	36.1	36.6
21	67.8	68.3	68.7
12-OMe	–	–	56.1
CO_2*Me*	52.5	52.2	52.8
CO_2Me	170.9	175.0	171.3
NCO_2*Me*	52.8	–	52.8
N*C*O_2Me	154.1	–	153.2

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

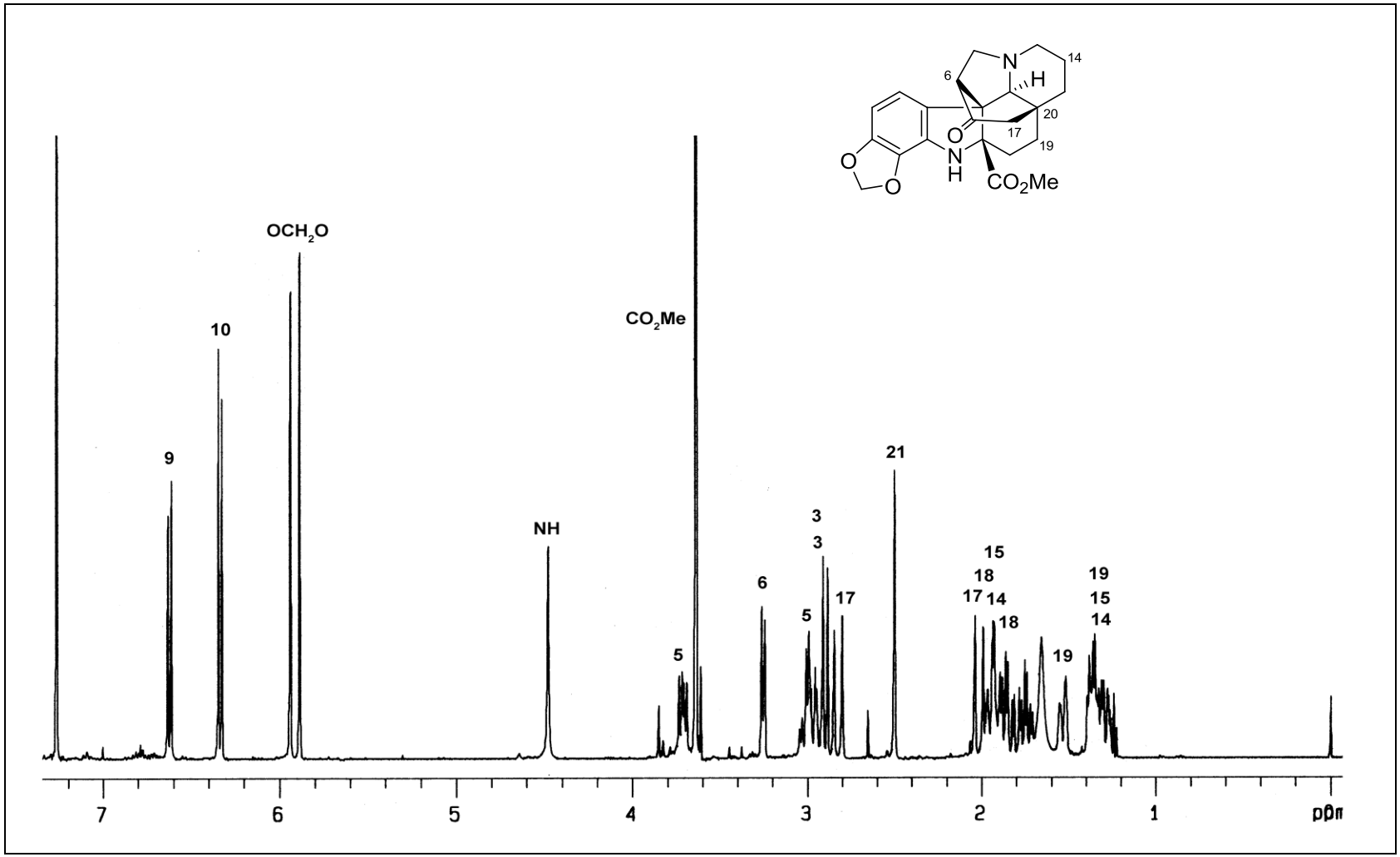


Figure 2.125: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (**95**)

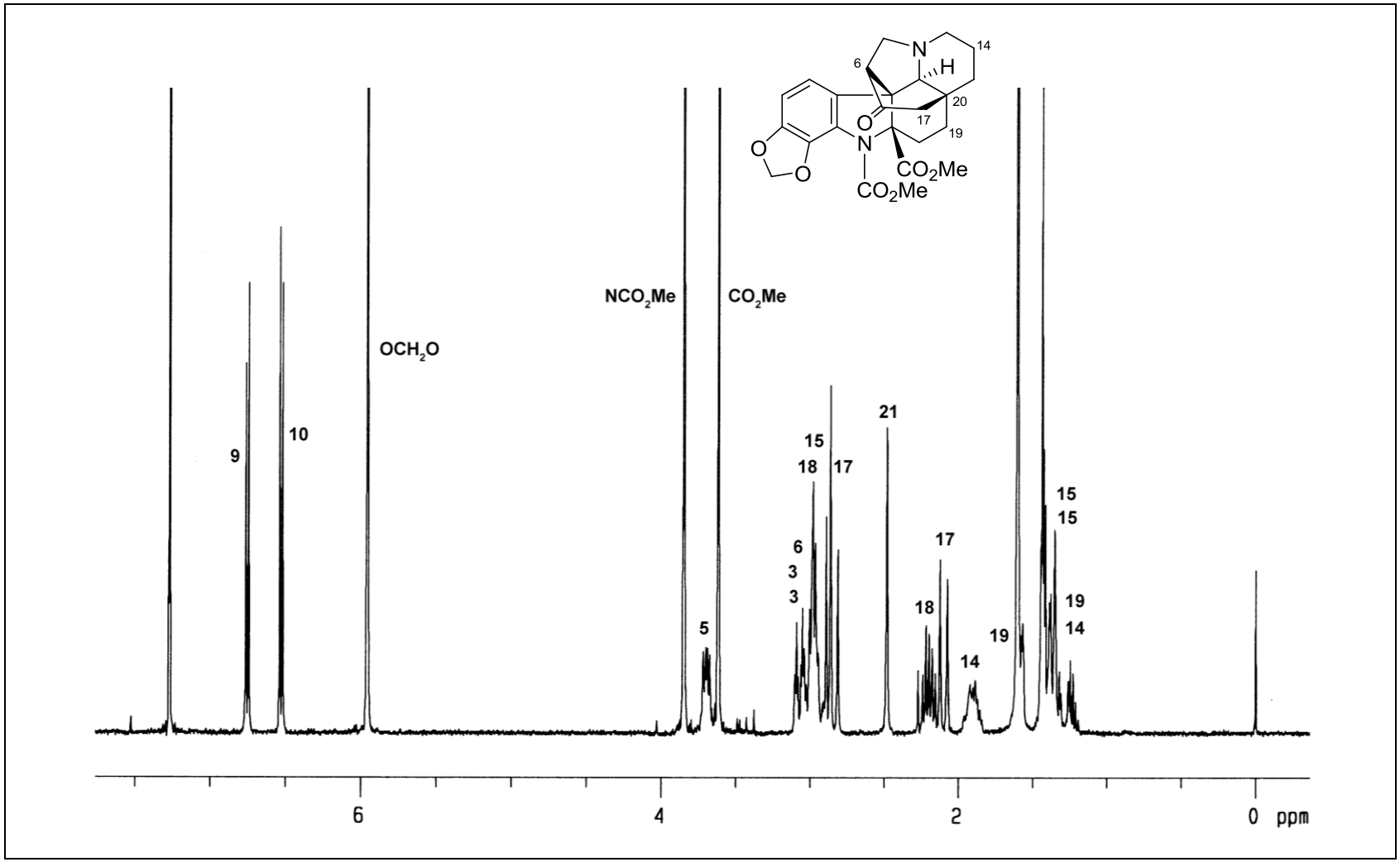


Figure 2.126: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of methyl 11,12-methylenedioxychanofruticosinate (**96**)

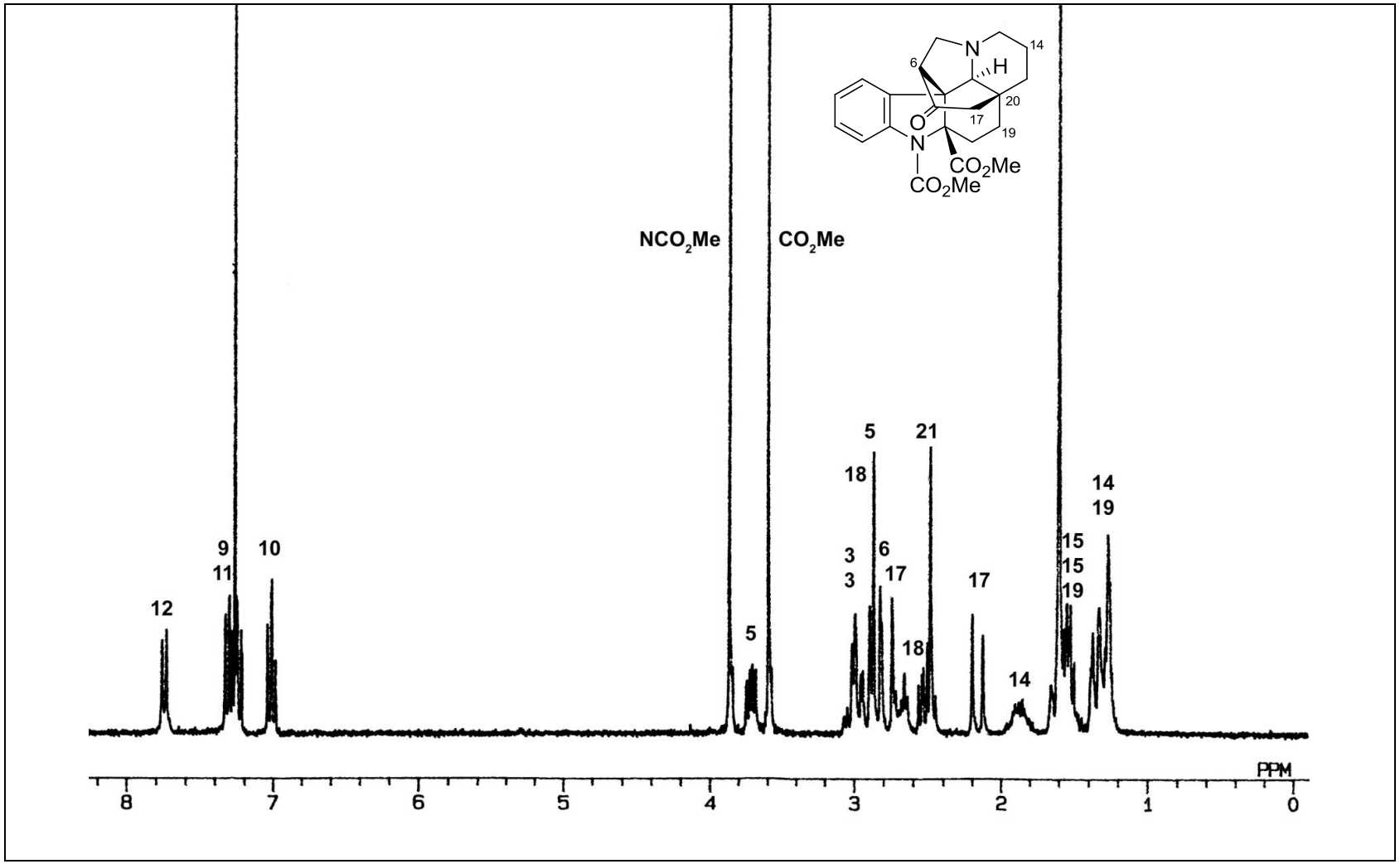


Figure 2.127: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of methyl chanofruticosinate (**97**)

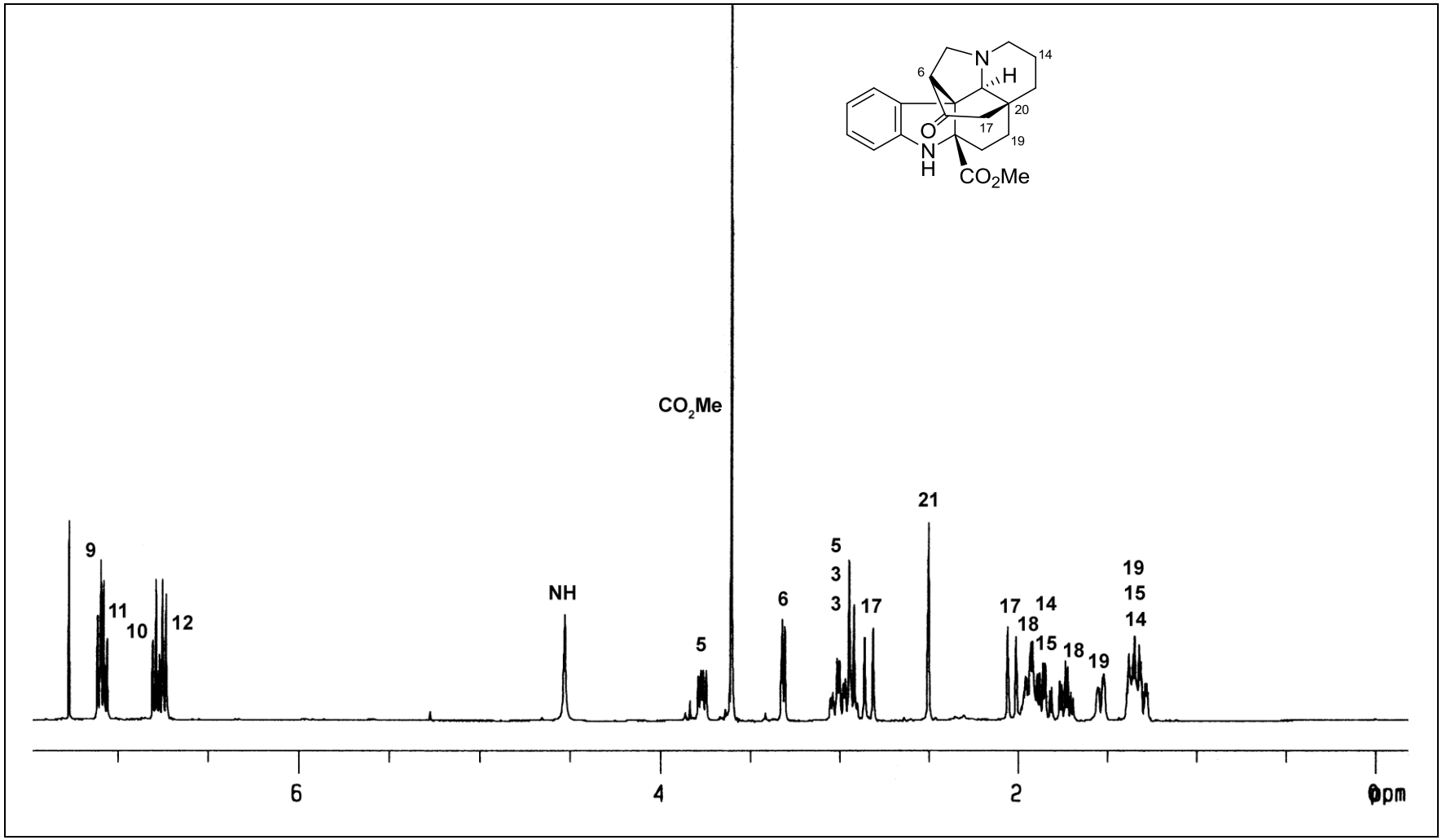


Figure 2.128: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)

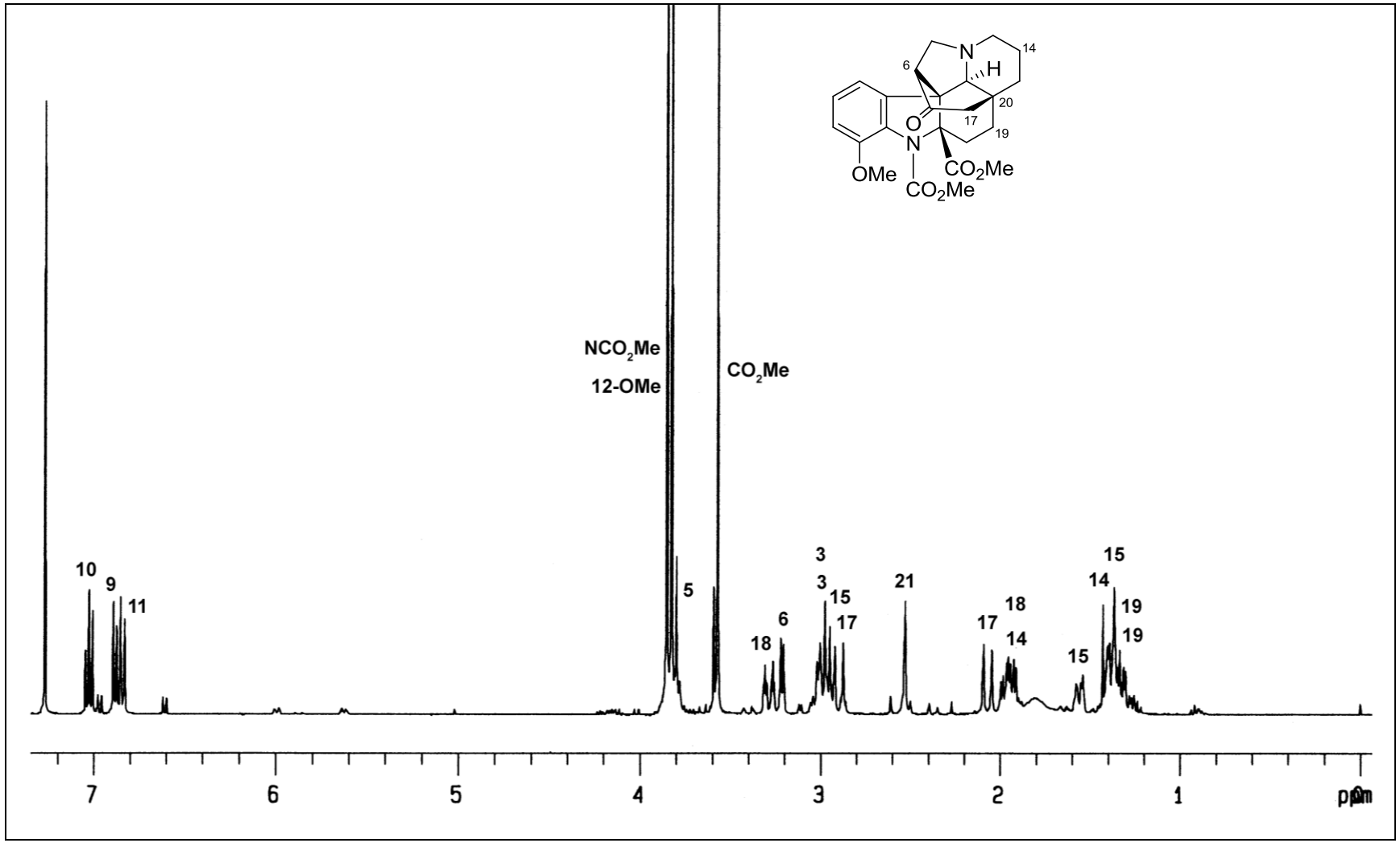


Figure 2.129: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of methyl 12-methoxychanofruticosinate (**99**)

2.2.10 Bisindole Alkaloids

2.2.10.1 (–)-Norpleiomutine (100)

The only known bisindole alkaloid isolated from the present study is (–)-norpleiomutine (**100**).[188,223,224] The ^{1}H NMR spectrum of **100** is shown in Figure 2.130, while the complete assignments of the NMR spectroscopic data of compound **100** are summarized in Table 2.67. Other data are given in the Experimental Section.

Table 2.67: ^{1}H and ^{13}C NMR Spectroscopic Data of (–)-Norpleiomutine (**100**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	66.8	2′	–	133.9
3	3.05 m 3.05 m	47.4	3′	2.49 br t (13) 2.62 m	44.4
5	3.05 m 3.35 m	50.8	5′	3.35 m 3.35 m	50.9
6	1.73 m 2.74 m	34.9	6′	2.62 m 3.05 m	17.0
7	–	58.1	7′	–	104.6
8	–	141.4	8′	–	128.4
9	7.17 s	120.0	9′	7.44 d (8)	117.6
10	–	134.5	10′	7.00 t (8)	118.9
11	6.90 d (8)	125.1	11′	6.83 t (8)	120.0
12	6.62 d (8)	111.0	12′	6.54 d (8)	112.1
13	–	148.5	13′	–	136.5
14	1.27 m 1.90 m	16.6	14′	1.38 m 1.77 m	20.7
15	1.30 m 1.62 br d (13)	36.3	15′	1.14 m 1.38 m	24.2
16	2.91 t (10)	43.7	16′	4.94 dd (11, 5)	55.9
17	1.38 m 2.76 m	33.0	17′	1.77 m 2.11 m	45.1
18	1.26 m 1.92 m	33.7	18′	0.87 t (7.5)	7.4
19	1.26 m 1.41 m	33.8	19′	1.49 m 2.17 m	28.7
20	–	31.6	20′	–	34.9
21	3.02 s	67.9	21′	4.03 br s	59.5
CO_2*Me*	3.02 s	51.9			
CO_2Me	–	174.7			

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, HMBC, and NOESY/DNOE.

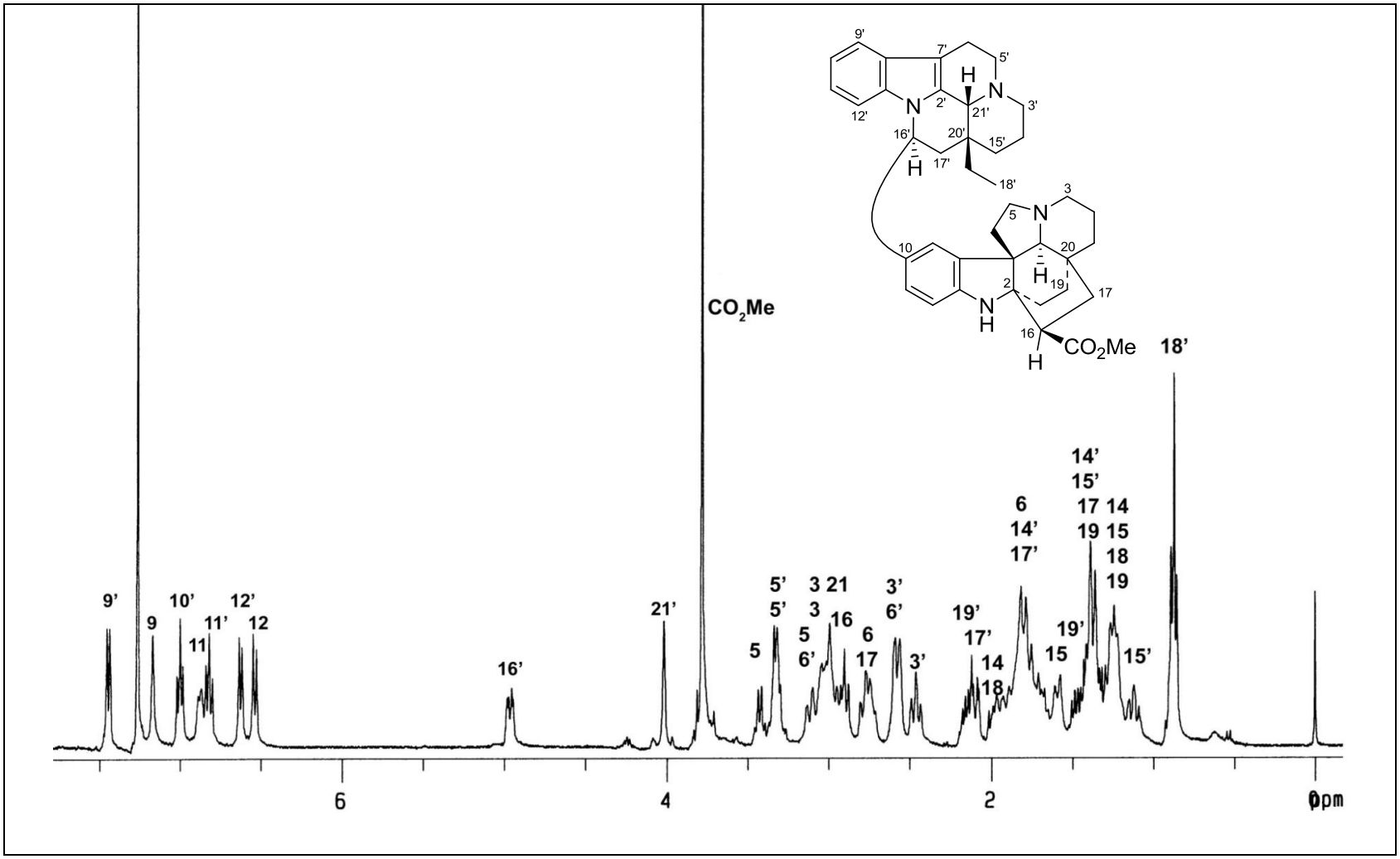


Figure 2.130: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (–)-norpleiomutine (**100**)

2.3 Comparison of Alkaloid Composition of *K. pauciflora* from Peninsular Malaysia (Malaya) and *K. pauciflora* from Malaysian Borneo (Sabah)

The present investigation of the stem-bark and leaves of *K. pauciflora* from Peninsular Malaysia (Malaya) has yielded a total of 50 alkaloids, of which 10 are new (**62**–**64**, **69**–**71**, **73**, **77**, **90**, **91**). Among the alkaloids obtained, eleven alkaloids are common in both the stem-bark and leave extracts (**14**, **25**, **43**, **63**, **78**, **79**, **81**, **83**, **85**, **95**, **96**). The alkaloids are constituted from 10 different subtypes, *viz.*, six leuconoxine-leuconolam-rhazinilam-type (**14**–**16**, **19**, **25**, **62**), 10 eburnane-type (**29**, **30**, **33**, **34**, **63**–**68**), seven corynanthean-type (**43**, **47**, **69**–**73**), seven aspidofractinine-type (**77**–**83**), three *Aspidosperma*-type (**74**–**76**), five kopsine-type (**84**–**88**), one *Strychnos*-type (**89**), five aspidospermatan-type (**90**–**94**), five methyl chanofruticosinate-type (**95**–**99**), and one bisindole (**100**) alkaloids. The major alkaloids found from this plant include the corynanthean alkaloid, tetrahydroalstonine (**43**), the aspidofractinine alkaloids, kopsinine (**79**), kopsamine (**80**), *N*(1)-decarbomethoxykopsamine (**81**), and the methyl chanofruticosinate alkaloids, methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxy-chanofruticosinate (**95**), methyl 11,12-methylenedioxychanofruticosinate (**96**), methyl chanofruticosinate (**97**), methyl *N*(1)-decarbomethoxychanofruticosinate (**98**), and methyl 12-methoxychanofruticosinate (**99**).

On the other hand, a total of 28 alkaloids were reported from *K. pauciflora* from Sabah, comprising six monoterpene-type (**121**–**126**), four eburnane-type (**29**, **33**, **34**, **66**), 12 aspidofractinine-type (**79**, **80**, **82**, **83**, **213**, **218**, **224**–**226**, **261**, **274**, **275**), one kopsidasine-type (**322**), four pauciflorine-type (**324**–**326**, **330**), and one bisindole (**100**)

alkaloids. Alkaloids of the monoterpene-type (**121**), pauciflorine-type (**324**), and aspidofractinine-type (**79**) predominate in this plant.

Alkaloids that are common to both plants include four of the eburnane-type (**29**, **33**, **34**, **66**), four aspidofractinine-type (**79**, **80**, **82**, **83**), and one bisindole (**100**) alkaloids. It is therefore apparent from the above comparison that the alkaloidal composition varies with the different locality, a feature which is becoming increasingly apparent from our ongoing investigation of the phytochemistry of the Malaysian Apocynaceae.

Table 2.68: Comparison of the Alkaloid Composition of *K. pauciflora* from Peninsular Malaysia (Terengganu) and *K. pauciflora* from Malaysian Borneo (Sabah)

Alkaloids	**Peninsular Malaysia, 2012**		**Malaysian Borneo, 1997**[219]	
	Bark	**Leaves**	**Bark**	**Leaves**
Monoterpene Alkaloids				
Kinabalurine A (**121**)				+
Kinabalurine B (**122**)				+
Kinabalurine C (**123**)				+
Kinabalurine D (**124**)				+
Kinabalurine E (**125**)				+
Kinabalurine F (**126**)				+
Leuconoxine-Leuconolam-Rhazinilam Alkaloids				
Leuconoxine (**14**)	+	+		
Leuconodine F (6-oxoleuconoxine) (**15**)		+		
Mersicarpine (**16**)		+		
Leuconolam (**19**)		+		
Rhazinilam (**25**)	+	+		
Compound **62** (New)		+		
Eburnane Alkaloids				
(+)-Eburnamonine (**29**)	+		+	
(+)-Eburnamenine (**30**)	+			
(+)-Isoeburnamine (**33**)	+		+	
(–)-Eburnamine (**34**)			+	

Table 2.68, continued

Alkaloids	**Peninsular Malaysia, 2012**		**Malaysian Borneo, 1997[219]**	
	Bark	**Leaves**	**Bark**	**Leaves**
Eburnane Alkaloids				
Compound **63** (New)	+	+		
Compound **64** (New)	+			
Larutenine (**65**)		+		
(+)-19-Oxoeburnamine (**66**)	+		+	
(–)-19(*R*)-Hydroxyisoeburnamine (**67**)	+			
(+)-19(*R*)-Hydroxyeburnamine (**68**)	+			
Corynanthe Alkaloids				
Tetrahydroalstonine (**43**)	+	+		
16(*R*)-19,20-*E*-Isositsirikine (**47**)		+		
Compound **69** (New)		+		
Compound **70** (New)		+		
Compound **71** (New)		+		
(–)-Catharinensine (**72**)		+		
Tetrahydroalstonine pseudoindoxyl (**73**) (New)		+		
Aspidofractinine Alkaloids				
11,12-Dimethoxykopsinaline (**77**) (New)	+			
Pseudokopsinine (**78**)	+	+		
Kopsinine (**79**)	+	+	+	
Kopsamine (**80**)	+		+	+
N(1)-Decarbomethoxykopsamine (**81**)	+	+		
Kopsilongine (**82**)	+		+	
Paucifinine (**83**)	+	+		+
Kopsamine *N*-oxide (**213**)			+	+
11-Methoxykopsilongine (*N*-methoxycarbonyl-11,12-dimethoxykopsinaline (**218**)			+	+
Paucifinine *N*-oxide (**224**)				+
Lahadinine A (**225**)				+
Lahadinine B (**226**)				+
N(1)-Methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine (**261**)			+	
Paucidactine A (**274**)				+
Paucidactine B (**275**)				+
***Aspidosperma* Alkaloids**				
(+)-Aspidospermidine (**74**)		+		
(+)-1,2-Dehydroaspidospermidine (**75**)		+		
(–)-Quebrachamine (**76**)		+		
Kopsine Alkaloids				
Kopsanone (**84**)	+			
11,12-Methylenedioxykopsine (**85**)	+	+		
12-Methoxykopsine (**86**)		+		

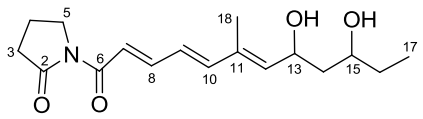
Table 2.68, continued

Alkaloids	**Peninsular Malaysia, 2012**		**Malaysian Borneo, 1997[219]**	
	Bark	**Leaves**	**Bark**	**Leaves**
Kopsine Alkaloids				
Kopsifine (**87**)	+			
N(1)-Decarbomethoxykopsifine (**88**)	+			
Kopsidasinine Alkaloids				
12-Methoxy-10-demethoxykopsidasinine (**322**)			+	
Pauciflorine Alkaloids				
Pauciflorine A (**324**)			+	+
Pauciflorine B (**325**)				+
Pauciflorine C (**326**)				+
Paucifoline (**330**)				+
***Strychnos* Alkaloids**				
Akuammicine (**89**)		+		
Aspidospermatan Alkaloids				
Andransinine (**90**) (New)		+		
Compound **91** (New)		+		
Condylocarpine (**92**)		+		
Precondylocarpine (**93**)		+		
Stemmadenine (**94**)		+		
Methyl chanofruticosinate Alkaloids				
Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (**95**)	+	+		
Methyl 11,12-methylenedioxychanofruticosinate (**96**)	+	+		
Methyl chanofruticosinate (**97**)		+		
Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)		+		
Methyl 12-methoxychanofruticosinate (**99**)		+		
Bisindole Alkaloids				
(–)-Norpleiomutine (**100**)	+		+	

2.4 Alkaloids from *Penicillium* sp. (CDA p48.3)

During this study many soil samples were collected from various locations, which were then cultured in order to isolate pure strains of microbes, including actinobacteria and fungi. The pure strains thus obtained, were then extracted and screened for the presence of potentially interesting secondary metabolites. Unfortunately however, despite a considerable number of sampling carried out, the chemical screening results were not encouraging, furnishing mainly long chain fatty acids and known diketopiperazines in most cases.

In one instance, a total of 15 different *Penicillium* strains were screened for their chemical constituents, of which only one of the strains (CDA p48.3) was found to produce a number of compounds. Seven alkaloids were subsequently obtained, of which three are new. These three new alkaloids are the variotin derivatives (**101**–**103**), which consist of a pyrrolidone moiety and a C_{12} side chain. The alkaloid composition of *Penicillium* sp. (CDA p48.3) is summarized in Table 2.69.



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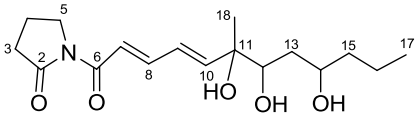
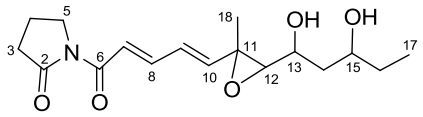
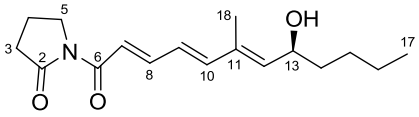


102



103



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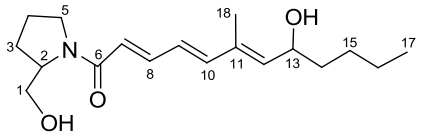
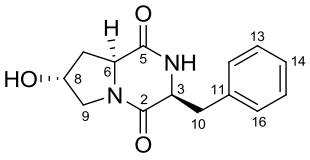
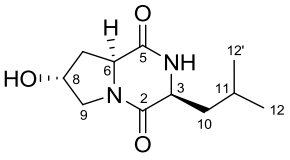


105



106



107

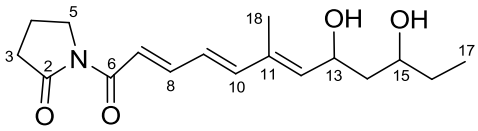
Table 2.69: Alkaloid Composition of *Penicillium* sp. (CDA p48.3)

Fungi	Alkaloid	Yield (g L^{-1})
Broth extract	Compound **101**	0.00177
(0.857 g)	Compound **102**	0.00040
	Compound **103**	0.00107
	Variotin (**104**)	0.00567
	Viriditin (**105**)	0.00253
	cyclo (L-Phenylalanine-*trans*-4-hydroxy-L-proline) (**106**)	0.00107
	cyclo (L-Leucine-*trans*-4-hydroxy-L-proline) (**107**)	0.00523

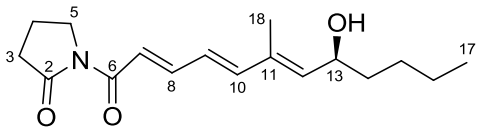
2.4.1 Variotin Alkaloids

2.4.1.1 Compound 101

Compound **101** was isolated as a light yellowish oil in minute amounts, with $[\alpha]_D$ −2 ($CHCl_3$, *c* 0.24). The UV spectrum of **101** showed absorption maxima at 225, 287, and 332 nm, while the IR spectrum indicated the presence of OH (3368 cm^{-1}) and lactam (1738 and 1679 cm^{-1}) functions. The carbon resonances observed at δ 167.3 and 176.3 in the ^{13}C NMR data (Table 2.71) confirmed the presence of two lactam carbonyl functions in **101**. The LSIMS of **101** showed an $[M + H]^+$ peak at *m*/*z* 308 and the HRLSIMS measurements gave the formula $C_{17}H_{25}NO_4$. The ^{13}C NMR data (Table 2.71) gave a total of 17 carbon resonances (two methyl, five methylene, seven methine, and three quaternary carbons) in agreement with the molecular formula.



101



104

The NMR data (Tables 2.70 and 2.71) of **101** were very similar to those of variotin (**104**),[385-387] except for some minor changes. The ^1H NMR spectrum (Figure 2.134) of **101** showed the presence of signals due to H(3) (δ 2.62, td, *J* = 8, 1.7 Hz), H(4) (δ 2.05, qu, *J* = 8 Hz), and H(5) (δ 3.87, td, *J* = 8, 1.7 Hz), indicating that the pyrrolidone moiety in variotin (**104**) was also present in compound **101**. Thus, the changes in **101** when compared to those of **104**, must be associated with the side chain branched from the nitrogen atom of the pyrrolidone ring. Detailed examination of the ^{13}C NMR data of **101**

revealed that the C(15) methylene carbon signal in **104** (δ 27.3) has shifted downfield to δ 73.4 in **101**, indicating that oxygenation has occurred at C(15) in **101**. This was supported by the COSY and HMQC data, which revealed a $CHCHCH_2CH$ fragment corresponding to the C(12)–C(13)–C(14)–C(15) unit in **101**, instead of a $CHCHCH_2CH_2$ unit in **104**.

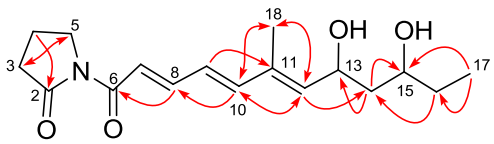
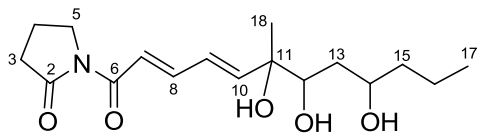


Figure 2.131: Selected HMBCs of **101**

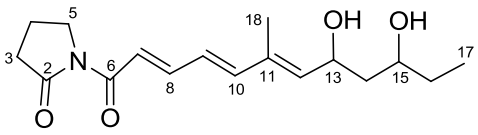
The placement of the hydroxy group at C(15) was further supported by the HMBC data (Figure 2.131), which showed three-bond correlation from H(17) to C(15). The structure deduced is entirely consistent with the rest of the HMBC data. Compound **101** is therefore 15-hydroxyvariotin.

2.4.1.2 Compound 102

Compound **102** was isolated as a light yellowish oil in minute amounts, $[\alpha]_D$ −6 ($CHCl_3$, *c* 0.04). The UV and IR spectra were similar to those of **101**, suggesting a variotin-type compound with similar functionalities. The LSIMS of **102** showed an $[M + H]^+$ peak at *m*/*z* 326 and the HRLSIMS measurements gave the formula $C_{17}H_{27}NO_5$.



102



101

The ^{1}H and ^{13}C NMR data (Tables 2.70 and 2.71) of **102** were generally similar to those of **101**, except for changes involving H(12), H(13), H(14), and H(15). Examination of the ^{13}C NMR data (Table 2.71) of **102** indicated the absence of signals due to the trisubstituted double bond corresponding to C(11)–C(12) in **101**, instead, two higher field signals were observed at δ 84.8 and 77.1, suggesting that the C(11)–C(12) double bond has been reduced and oxygenation had occured at C(11) and C(12), respectively. The observed downfield shift of the C(14) carbon signal from δ 42.0 in **101** to 76.3 in **102**, indicated the placement of the third hydroxyl group at C(14) in **102**.

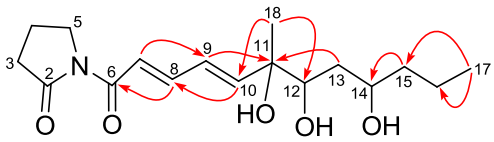


Figure 2.132: Selected HMBCs of **102**

The location of the hydroxy functions at C(11), C(12), and C(14) in **102** were further supported by the HMBC data (Figure 2.132), which showed three-bond correlations from H(9) and H(13) to C(11), and from H(18) to C(12). The structure proposed is in complete accord with the HMBC data.

2.4.1.3 Compound 103

Compound **103** was obtained in minute amounts as a light yellowish oil, $[\alpha]_D$ +7 ($CHCl_3$, *c* 0.09). The UV and IR spectra of **103** were similar to those of **101** and **102**, suggesting a variotin-type compound with similar functionalities. The LSIMS of **103** showed an $[M + H]^+$ peak at *m/z* 324, 16 mass units higher than that of **101**, and the HRLSIMS measurements established the molecular formula as $C_{17}H_{25}NO_5$. The NMR data (Tables 2.70 and 2.71) of **103** is very similar to those of **101**, except for changes involving H(12), C(11), and C(12) in **103**. As in the case of **102**, two higher field signals were observed in **103** at δ 76.9 and 73.0, corresponding to C(11) and C(12), respectively, indicating that the trisubstituted C(11)–C(12) double bond present in **101**, was absent in **103**. Thus, the additional oxygen atom must be attached to C(11) and C(12) to form an epoxide ring in **103**. The placement of the epoxide function at C(11)–C(12) was further confirmed by the HMBC data (Figure 2.133), which showed three-bond correlations from H(9) to C(11), and from H(18) to C(12).

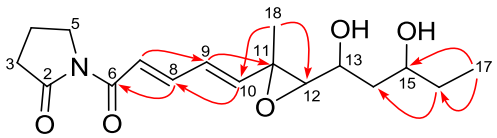


Figure 2.133: Selected HMBCs of **103**

The relative configurations at the various stereogenic centers in compounds **101**–**103** were not determined due to the small amounts obtained.

Table 2.70: ^{1}H NMR Spectroscopic Data of Compounds **101**–**103**[a]

H	**101**	**102**	**103**
3	2.62 td (8, 1.7)	2.62 t (8)	2.63 t (8)
4	2.05 qu (8)	2.05 qu (8)	2.05 qu (8)
5	3.87 td (8, 1.7)	3.87 t (8)	3.87 t (8)
7	7.36 dd (15, 1.5)	7.32 d (15)	7.31 d (15)
8	7.49 ddd (15, 11, 1.5)	7.42 ddd (15, 11, 0.5)	7.47 dd (15, 10)
9	6.45 ddd (15, 11, 1.5)	6.49 dd (15, 11)	6.44 dd (15, 10)
10	6.60 d (15)	6.14 d (15)	6.37 d (15)
12	5.68 d (8.3)	4.10 m	3.53 br d (3.7)
13	4.77 m	1.67 m	4.07 br q (3.7)
		2.31 ddd (13, 7.6, 6)	
14	1.59 m	3.96 q (7)	1.52 m
	1.64 m		1.76 ddd (14, 11.5, 3.5)
15	3.80 m	1.61 m	3.76 m
		1.67 m	
16	1.50 m	1.45 m	1.45 m
	1.50 m	1.45 m	1.60 m
17	0.93 t (7.3)	0.95 t (7)	0.98 t (7)
18	1.85 s	1.32 s	1.29 s

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

Table 2.71: ^{13}C NMR Spectroscopic Data of Compounds **101**–**103**[a]

C	**101**	**102**	**103**
2	176.3	175.7	176.0
3	33.8	34.0	34.1
4	17.0	17.3	17.2
5	45.7	45.9	46.0
6	167.3	166.4	167.0
7	121.5	122.3	121.9
8	145.7	145.0	145.6
9	126.6	126.9	127.0
10	145.5	147.3	146.8
11	134.2	84.8	76.9
12	138.9	77.1	73.0
13	69.1	40.1	69.2
14	42.0	76.3	33.1
15	73.4	39.5	67.6
16	30.6	19.4	29.1
17	9.5	14.2	10.2
18	12.6	21.3	26.4

[a] $CDCl_3$, 100 MHz; assignments based on HMQC and HMBC.

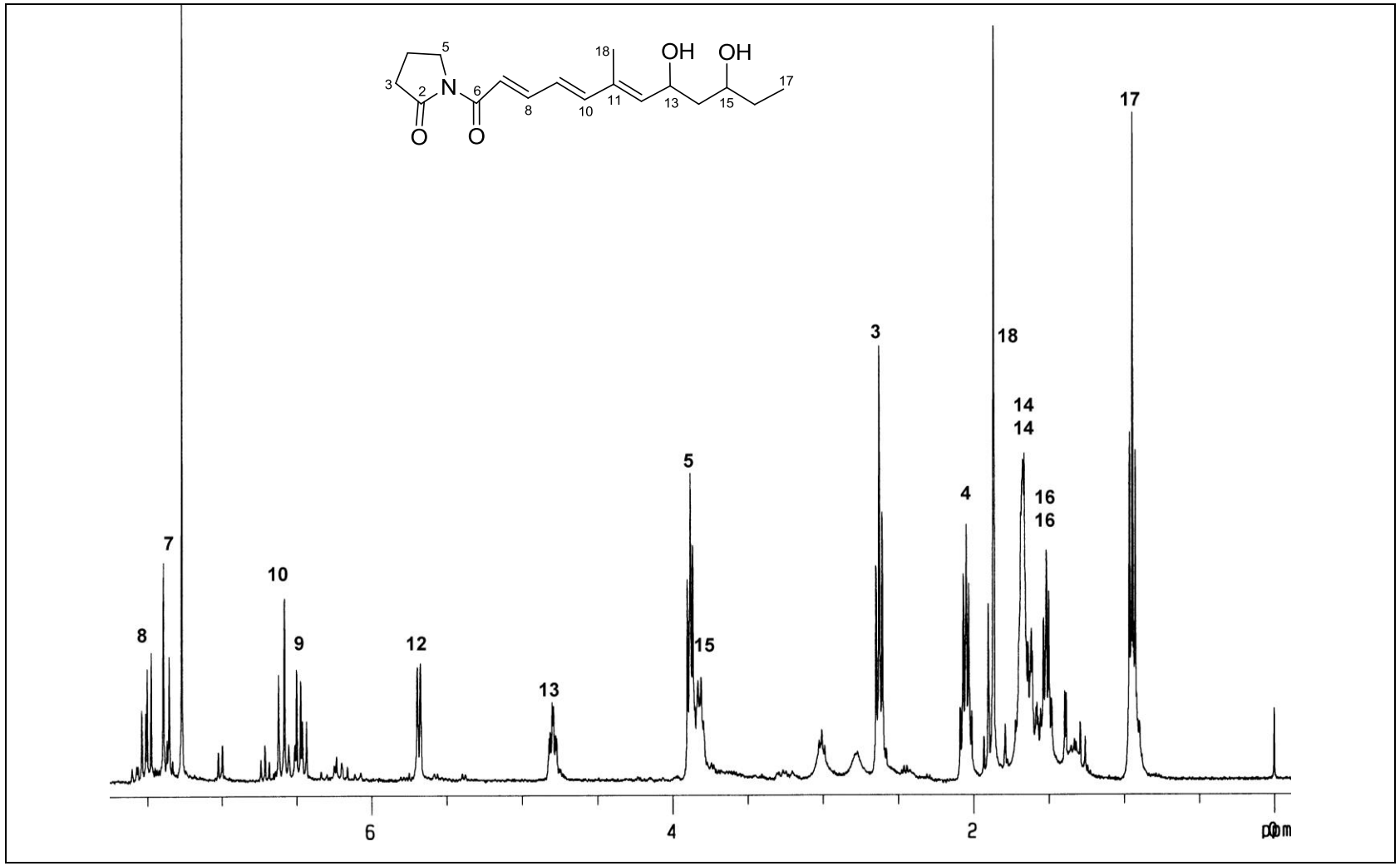


Figure 2.134: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of compound **101**

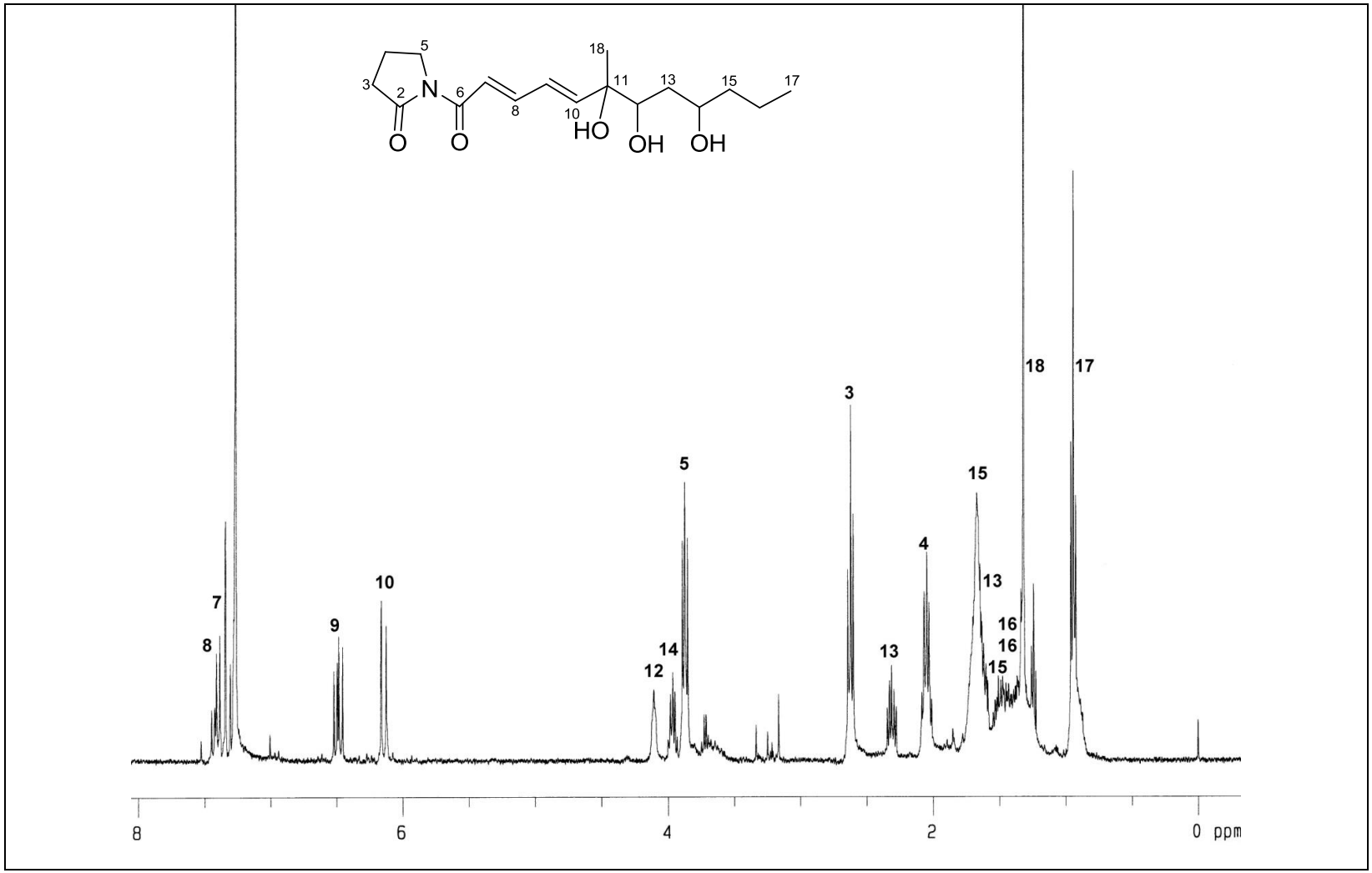


Figure 2.135: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of compound **102**

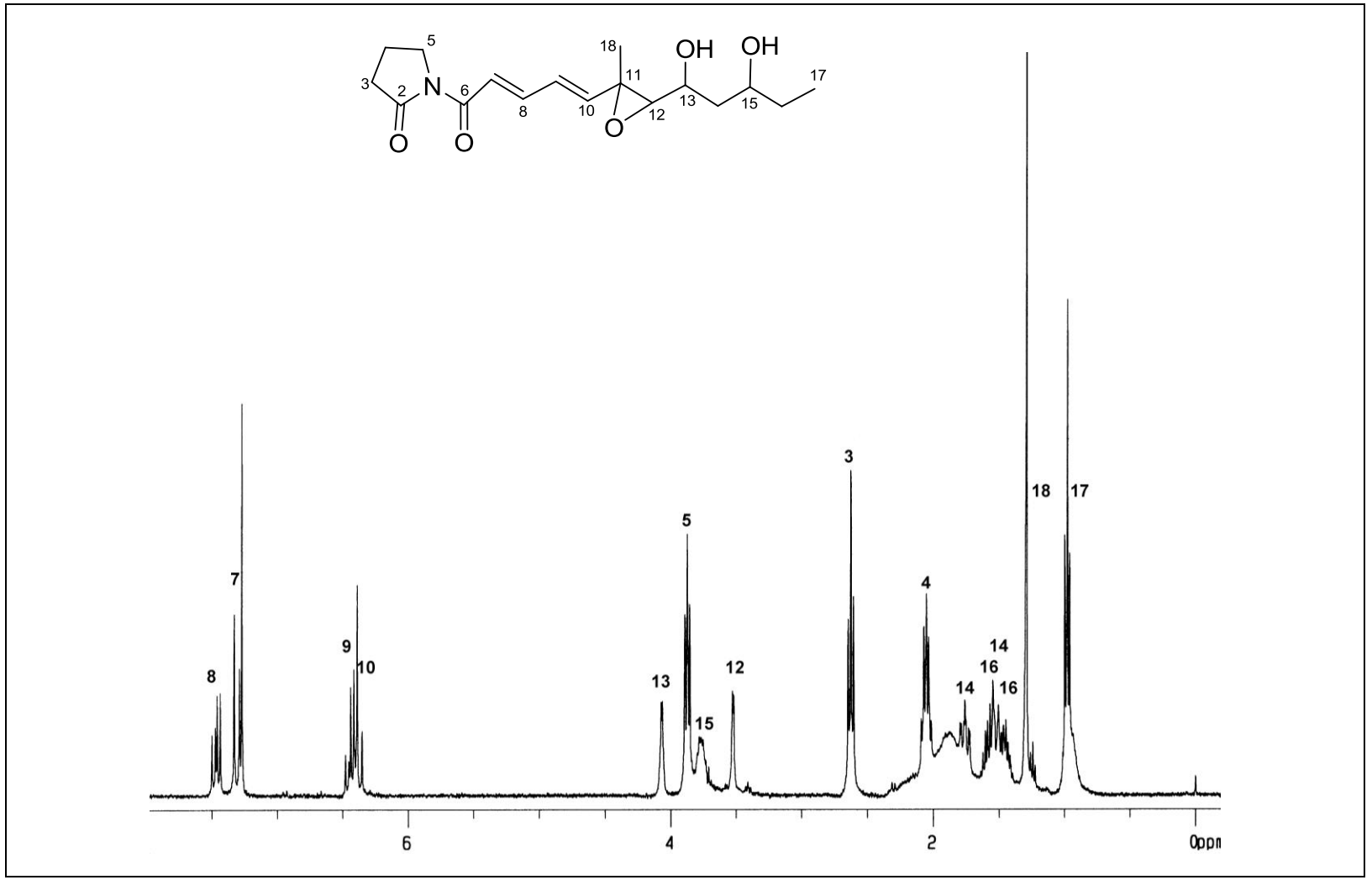


Figure 2.136: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of compound **103**

2.4.1.4 Variotin (104) and Viriditin (105)

Two known alkaloids belonging to this group, *viz.*, variotin (**104**)[385-387] and viriditin (**105**)[388] were also isolated. The ^{1}H NMR spectra of these compounds are shown in Figures 2.137 and 2.138, while the NMR spectroscopic data are summarized in Table 2.72. Other data are given in the Experimental Section.

Table 2.72: ^{1}H and ^{13}C NMR Spectroscopic Data of Variotin (**104**) and Viriditin (**105**)[a]

Position	**104**		**105**	
	δ_H	δ_C	δ_H	δ_C
1	–	–	3.66 m	66.9
			3.66 m	
2	–	175.5	4.32 m	61.2
3	2.62 t (8)	33.8	1.67 m	28.1
			2.05 m	
4	2.04 qu (8)	17.0	4.00 m	24.3
5	3.87 t (8)	45.7	3.60 m	48.0
6	–	166.2	–	167.4
7	7.36 d (15)	121.4	6.23 d (15)	120.8
8	7.50 dd (15, 11)	145.7	7.38 dd (15, 11)	143.4
9	6.45 dd (15, 11)	126.4	6.37 dd (15, 11)	125.9
10	6.61 d (15)	145.8	6.57 d (15)	144.6
11	–	134.4	–	134.5
12	5.67 d (8.5)	139.8	5.65 d (8.6)	139.2
13	4.49 dd (15, 7)	68.2	4.50 dd (15, 7)	68.4
14	1.49 m	36.9	1.49 m	37.1
	1.64 m		1.63 m	
15	1.33 m	27.3	1.33 m	27.4
	1.33 m		1.33 m	
16	1.33 m	22.5	1.33 m	22.6
	1.33 m		1.33 m	
17	0.90 t (7)	13.9	0.90 t (7)	14.0
18	1.84 s	12.6	1.85 s	12.7
OH	2.44 br s	–	5.34 br s	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

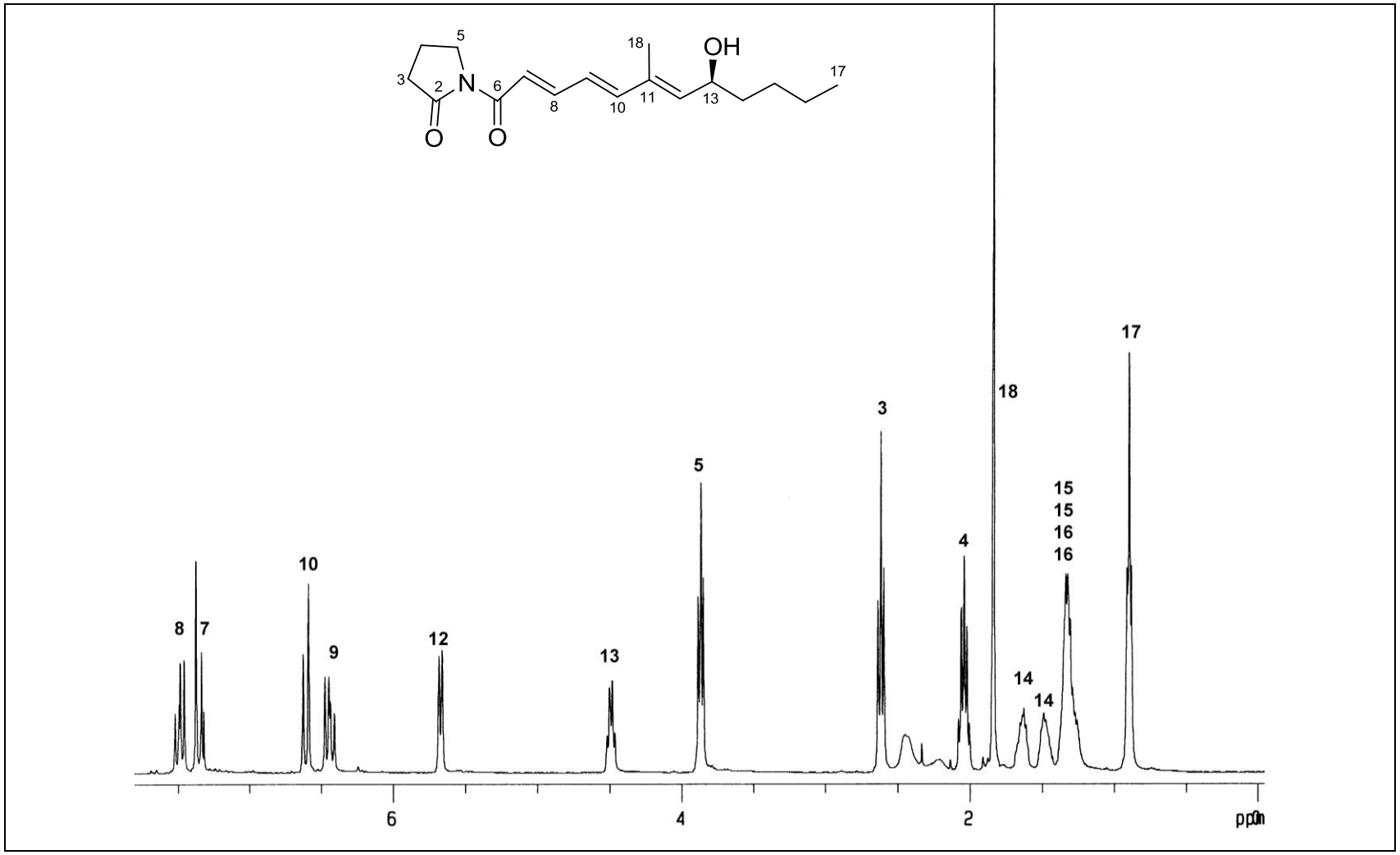


Figure 2.137: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of variotin (**104**)

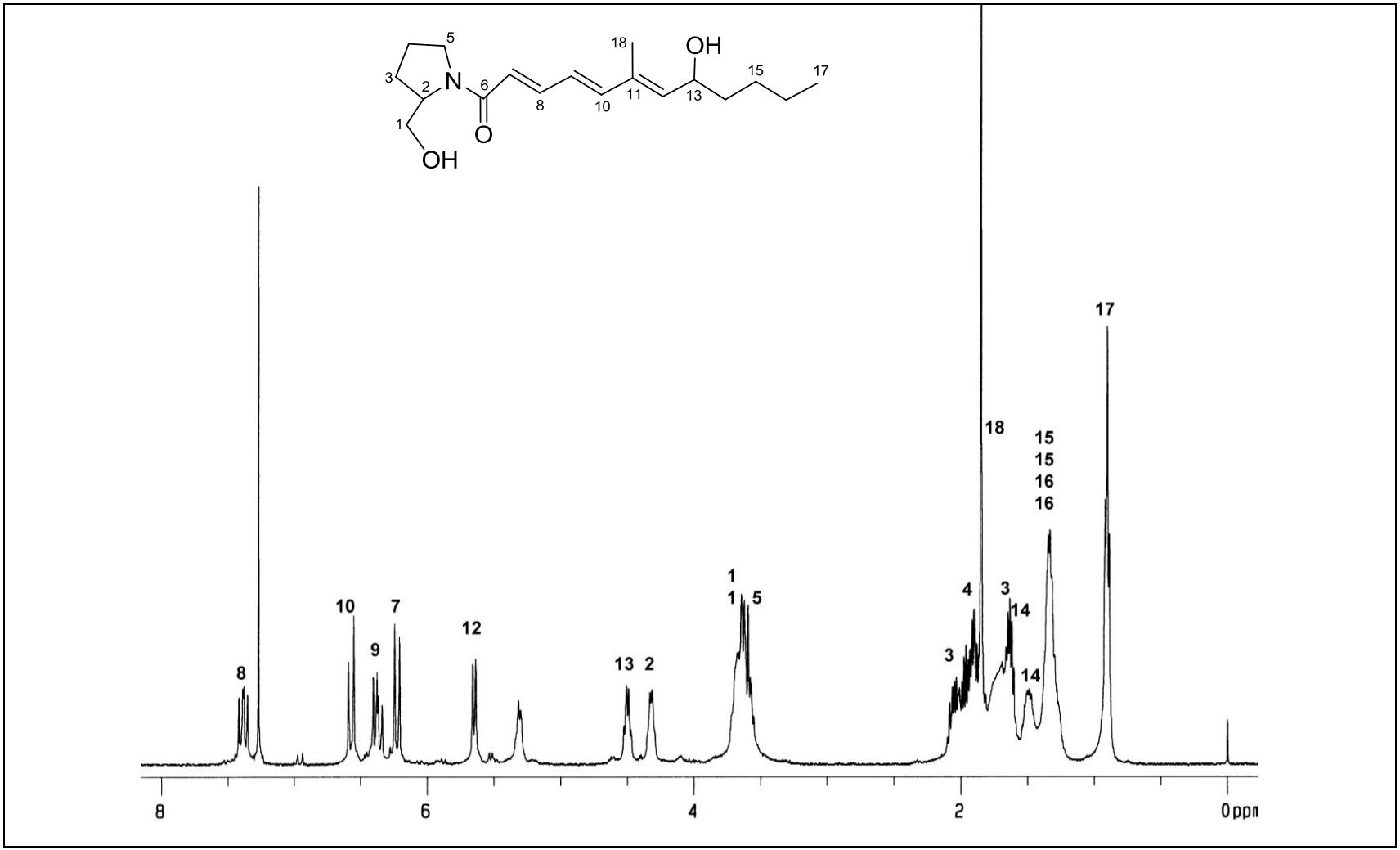


Figure 2.138: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of viriditin (**105**)

2.4.2 Diketopiperazine Alkaloids

2.4.2.1 *cyclo* (L-Phenylalanine-*trans*-4-hydroxy-L-proline) (106) and *cyclo* (L-Leucine-*trans*-4-hydroxy-L-proline) (107)

Two known alkaloids belonging to this group, *viz.*, *cyclo* (L-phenylalanine-*trans*-4-hydroxy-L-proline) (**106**)[389,390] and *cyclo* (L-leucine-*trans*-4-hydroxy-L-proline) (**107**)[390-392] were isolated. The ^{1}H NMR spectra of these compounds are shown in Figures 2.139 and 2.140, while the NMR spectroscopic data are summarized in Table 2.73. Other data are given in the Experimental Section.

Table 2.73: ^{1}H and ^{13}C NMR Spectroscopic Data of *cyclo* (L-Phenylalanine-*trans*-4-hydroxy-L-proline) (**106**) and *cyclo* (L-Leucine-*trans*-4-hydroxy-L-proline) (**107**)[a]

Position	**106**		**107**	
	δ_H	δ_C	δ_H	δ_C
2	–	165.2	–	166.5
3	4.32 dd (11, 3)	56.1	4.06 dd (9, 3.5)	53.3
5	–	169.8	–	170.9
6	4.47 dd (11, 6)	57.4	4.49 dd (13, 6)	57.3
7	2.04 ddd (13, 11, 4) 2.36 dd (13, 6)	37.6	2.11 td (13, 4) 2.36 dd (13, 6)	37.1
8	4.57 t (4)	68.0	4.51 m	68.0
9	3.62 dd (13, 4) 3.78 dd (13, 4.6)	54.4	3.53 d (13) 3.66 dd (13, 4)	54.2
10	2.79 dd (14, 11) 3.58 d (14)	36.6	1.53 ddd (14, 10, 5) 2.01 ddd (14, 10, 4)	38.3
11	–	135.7	1.80 m	24.5
12	7.36 m	129.2	0.96 d (6.6)	21.2
12′	–	–	1.00 d (6.6)	23.1
13	7.24 m	129.2	–	–
14	7.29 m	127.5	–	–
15	7.24 m	129.2	–	–
16	7.36 m	129.2	–	–
NH	5.70 br s	–	6.68 br s	–

[a] $CDCl_3$, 400 MHz (^{1}H), 100 MHz (^{13}C); assignments based on COSY, HMQC, and HMBC.

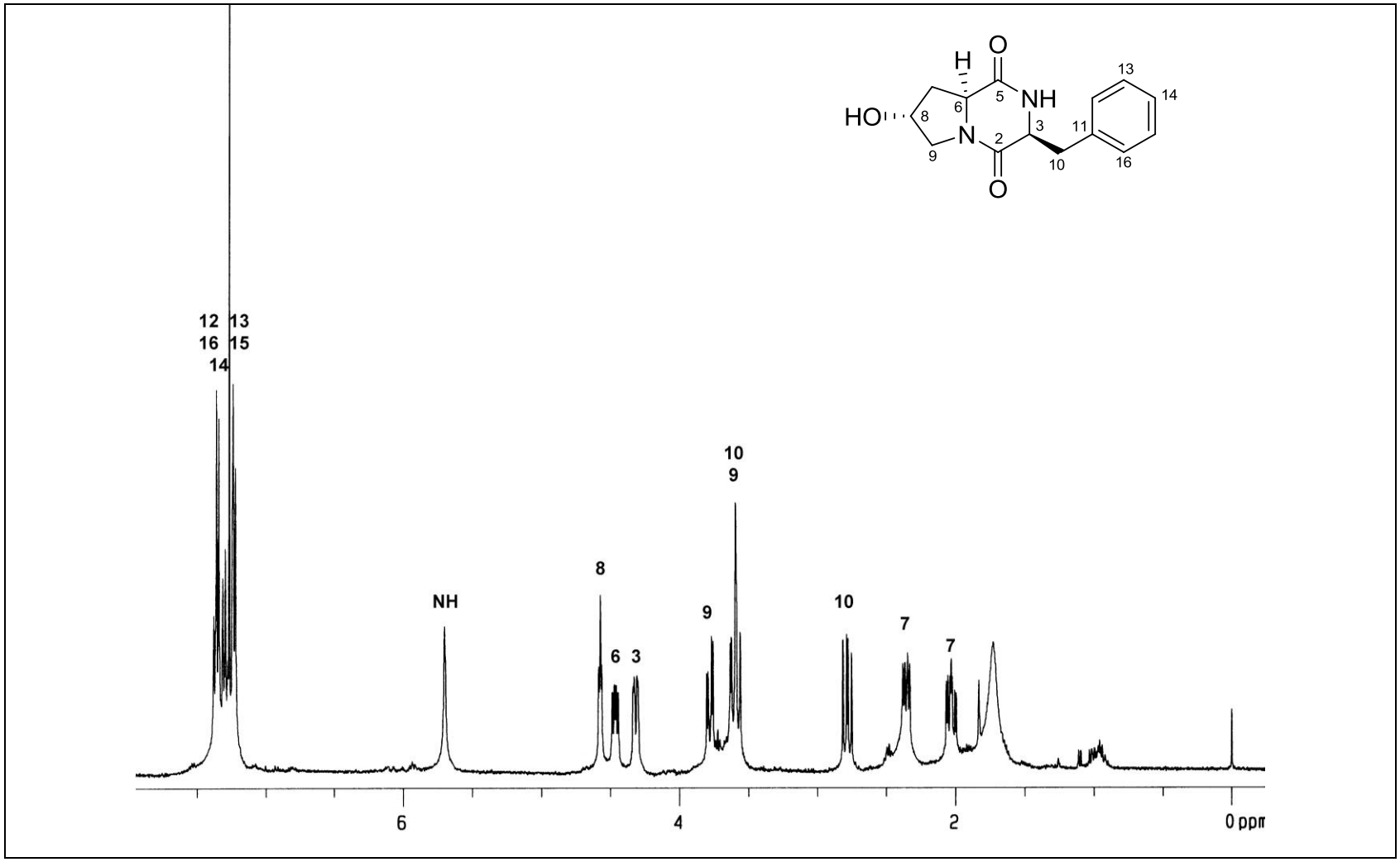


Figure 2.139: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *cyclo* (L-phenylalanine-*trans*-4-hydroxy-L-proline) (**106**)

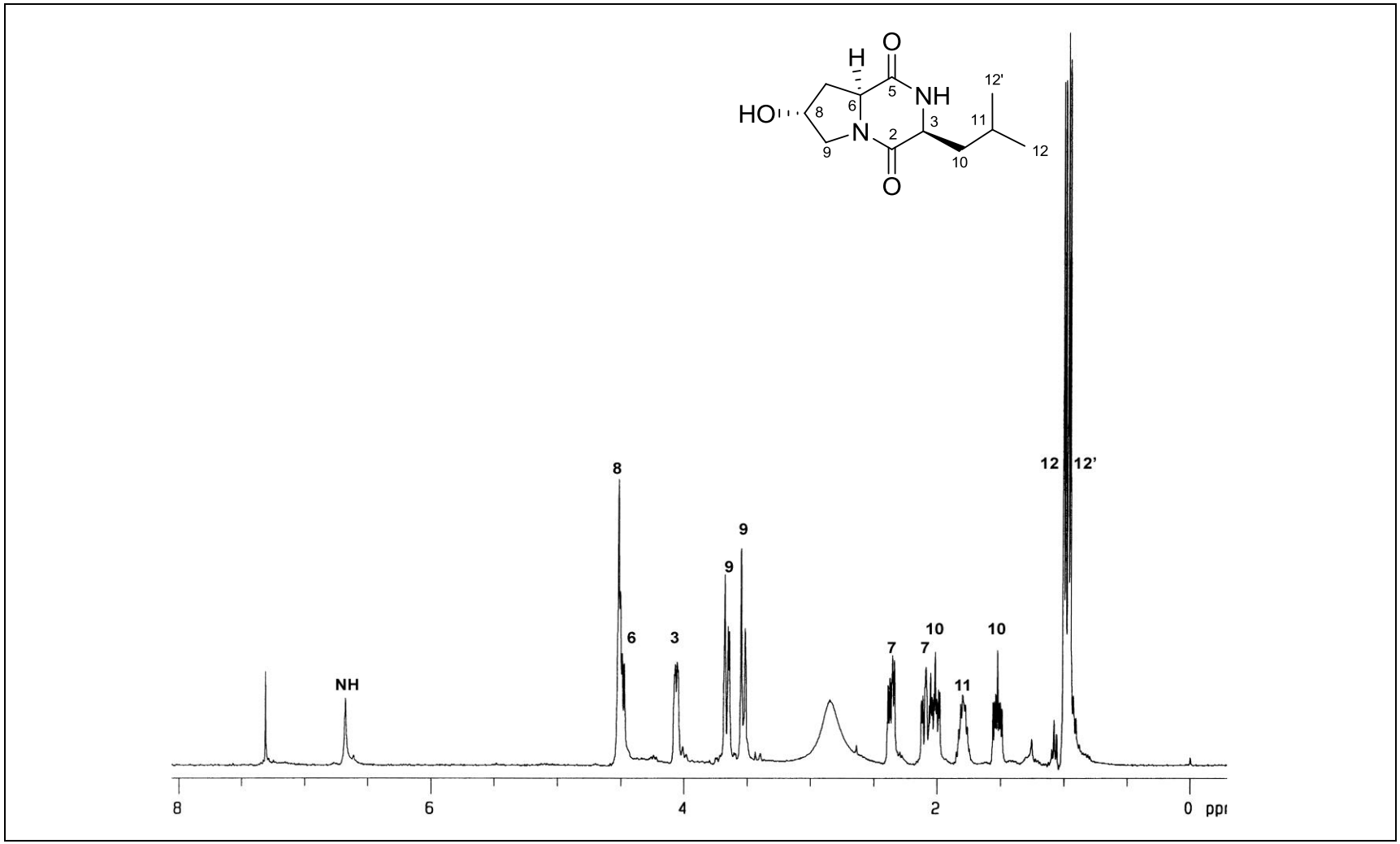


Figure 2.140: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *cyclo* (L-leucine-*trans*-4-hydroxy-L-proline) (**107**)

2.5 Biological Activity

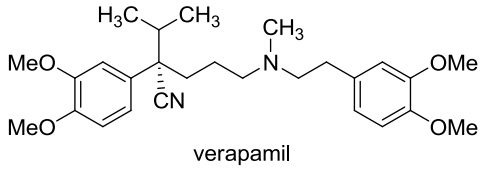
2.5.1 General

Alkaloids are interesting substances due to their multiple pharmacological activities. Thus, alkaloids isolated from the present study were screened for their biological activity, in particular for their cytotoxic effects, including their potential in reversing multidrug resistance (MDR) in drug-resistant tumor cells. This part of the work was carried out by Dr. K. Komiyama (Kitasato University, Japan) and his associates (Iwaki Meisei University, Japan).

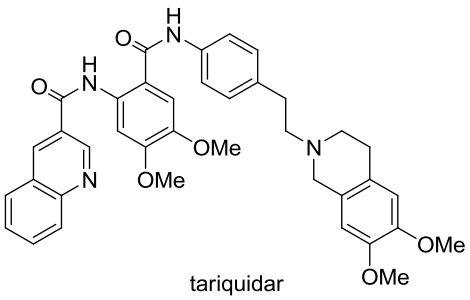
2.5.2 Cytotoxicity and Reversal of Multidrug Resistance (MDR)

Cancer represents one of the major causes of deaths worldwide. The development of new anticancer drugs as well as more effective treatment strategies, are therefore of great importance in drug discovery and clinical therapy. However, multidrug resistance (MDR) of cancer cells is one of the major obstacles to successful chemotherapeutic treatment of cancer. MDR is typically defined as the ability of a living cell to show resistance to a wide variety of structurally and functionally unrelated compounds, *e.g.*, taxanes (paclitaxel and docetaxel), *Vinca* alkaloids (vincristine and vinblastine), anthracyclines (doxorubicin and daunorubicin), and epipodophyllotoxins (etoposide and teniposide). MDR is usually associated with the over expression of P-glycoprotein (a multidrug resistant protein or ATP-dependent membrane transporter that acts as a drug efflux pump), resulting in increased efflux of chemotherapy from cancer cells.[393,394] One

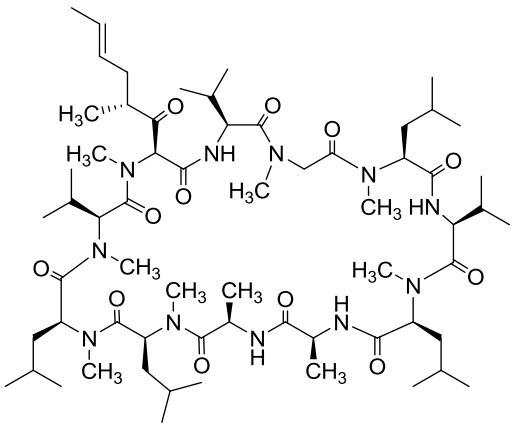
approach to counteract the mechanisms of drug resistance is to develop pharmacological agents (modulators of MDR, also known as chemosensitizers) that are devoid of cytotoxicities but are capable of inhibiting the functions of these membrane-bound proteins in tumor cells. When a modulator is present in the growth medium the sensitivity of the resistant cells to the oncolytic can be enhanced by inhibiting the efflux mechanism so that cells accumulate a higher intracellular concentration of the drug, thereby becoming more drug-sensitive. The Tsuruo group was the first to demonstrate that the sensitivity of P-gp-expressing multidrug-resistant cells was enhanced by the presence of the calcium channel blocker, verapamil.[395] Nowadays, one of the most promising P-gp inhibitors is the anthranilic acid derivative, tariquidar[396,397] (third-generation agent), which binds with high affinity to the P-gp transporter and potently inhibits its activity. The inhibitory effects of tariquidar on the P-gp transporter pump greatly exceed those of the phenylalkylamine derivative, verapamil (first-generation agent) and the cyclosporin derivative, valspodar (second-generation agent) with respect to potency and duration of action.[394] However, the mechanisms by which these drugs reverse MDR is not fully understood, and to date there are no MDR reversal agents available clinically (due to their toxicity), although several are currently undergoing clinical evaluation for the treatment of resistant tumors.[398-408]



verapamil



tariquidar



valspodar

As part of the group's ongoing search for new bioactive principles from plants and microorganisms, alkaloids obtained from the present study were screened for their cytotoxic effects against several cancer cell lines (KB and Jurkat) as well as their potential in reversing multidrug resistance (MDR) in drug-resistant KB cells. KB and Jurkat refer to the human oral epidermoid carcinoma and human T-cell-leukemia cell lines, respectively. The alkaloids were tested at an initial concentration of 25 μg/mL and the IC_{50} values were then determined for the more active compounds and the results are presented in Table 2.74.

5,21-Dihydrorhazinilam *N*-oxide (**23**), leucophyllidine (**36**),[137] and leucoridine A (**39**)[138] isolated from the stem-bark extract of *L. griffithii*, were found to display strong cytotoxicity toward drug-sensitive and drug-resistant KB cells. Other alkaloids such as leuconodine B (**10**), leuconodine D (**12**), *nor*-rhazinicine (**22**), leuconoline (**37**),[135] leucofoline (**38**),[135] and leucoridines B–D (**40**–**42**)[138] showed moderate cytotoxicity toward KB cells. Leuconicines A–B (**2**–**3**)[134] showed strong activity in reversing MDR in vincristine-resistant KB cells, while leuconicines C–E (**4**–**6**),[134] and leuconodine E (**13**) showed only moderate activity. Among the new alkaloids, leucolusine (**1**),[136] leuconicines F–G (**7**–**8**), leuconodine A (**9**), leuconodine C (**11**), 3,14-dehydroleuconolam (**18**), and (–)-eburnamaline (**28**),[134] did not show any appreciable bioactivity against KB cells. Leuconicines A–B (**2**–**3**) and leuconodine F (**15**) were found to be inactive when tested against Jurkat cells.

The stem-bark extract of *K. pauciflora* has yielded two new eburnane alkaloids (compounds **63** and **64**) and one new aspidofractinine derivative (11,12-

dimethoxykopsinaline (**77**)). Compound **64** showed weak ability in reversing multidrug resistance in vincristine-resistant KB cells while compounds **63** and **77** are inactive toward KB cells.

The corynanthean oxindole compound, **71**, and andransinine (**90**) isolated from the leaf extract of *K. pauciflora* were found to be highly effective in circumventing MDR in vincristine-resistant KB cells, while compounds **62** and **91** showed moderate activity in reversing multidrug resistance in vincristine-resistant KB cells. The only corynanthean-type pseudoindoxyl obtained from this plant, tetrahydroalstonine pseudoindoxyl (**73**) is inactive towards KB cells.

Variotin (**104**), isolated from *Penicillium* sp. (CDA p48.3) is inactive towards KB cells. The variotin derivatives, compounds **101**–**103**, were not evaluated due to the limited amounts obtained, and the instability of these compounds which leads to decomposition.

Table 2.74: Cytotoxic Effects of Alkaloids Isolated from *L. griffithii*, *K. pauciflora*, and *Penicillium* sp. (CDA p48.3)

Compound	IC_{50}, μg/mL (μM)			
	KB/S	KB/VJ300	KB/VJ300[a]	Jurkat
Alkaloids from *L. griffithii* (stem-bark)				
Leucolusine (**1**)	>25	>25	>25	
Leuconicine A (**2**)	>25	>25	2.57 (7.12)	>25
Leuconicine B (**3**)	>25	>25	1.98 (5.27)	>25
Leuconicine C (**4**)	>25	>25	3.86 (10.75)	
Leuconicine D (**5**)	>25	>25	4.62 (12.35)	
Leuconicine E (**6**)	>25	>25	13.52 (37.56)	
Leuconicine F (**7**)	>25	>25	>25	
Leuconicine G (**8**)	>25	>25	>25	
Leuconodine A (**9**)	>25	>25	>25	
Leuconodine B (scholarisine G) (**10**)	13.96 (42.82)	17.81 (54.63)	16.21 (49.72)	
Leuconodine C (**11**)	>25	>25	>25	
Leuconodine D (**12**)	17.90 (60.47)	11.50 (38.85)	3.95 (13.34)	19.80 (66.89)
Leuconodine E (**13**)	>25	>25	9.34 (29.94)	
Leuconoxine (**14**)	>25	>25	>25	
Leuconodine F (6-oxoleuconoxine) (**15**)	>25	>25	>25	>25
3,14-Dehydroleuconolam (**18**)	>25	>25	>25	
Nor-rhazinicine (**22**)	12.51 (42.55)	7.06 (24.01)	4.81 (16.36)	
5,21-Dihydrorhazinilam *N*-oxide (**23**)	1.14 (3.65)	1.53 (4.90)	1.75 (5.61)	
Rhazinilam (**25**)	0.19 (0.65)	0.25 (0.85)	0.34 (1.16)	
Rhazinal (**26**)	0.24 (0.75)	0.25 (0.78)	0.30 (0.93)	
Rhazinicine (**27**)	1.25 (4.06)	2.50 (8.12)	1.85 (6.01)	
(–)-Eburnamaline (**28**)	>25	>25	>25	
Leucophyllidine (**36**)	2.95 (5.16)	2.92 (5.10)	0.91 (1.59)	
Leuconoline (**37**)	11.46 (17.74)	12.17 (18.84)	9.33 (14.44)	
Leucofoline (**38**)	12.90 (23.20)	13.15 (23.65)	0.59 (1.06)	
Leucoridine A (**39**)	0.57 (1.03)	2.39 (4.30)	0 (0)	
Leucoridine B (**40**)	11.59 (20.92)	12.05 (21.75)	12.41 (22.40)	
Leucoridine C (**41**)	10.91 (19.01)	11.80 (20.56)	11.26 (19.62)	

Table 2.74, continued

Compound	IC_{50}, μg/mL (μM)			
	KB/S	KB/VJ300	KB/VJ300[a]	Jurkat
Leucoridine D (**42**)	12.53 (22.46)	13.29 (23.82)	1.50 (2.69)	
16(*S*)-19,20-*E*-Isositsirikine (**48**)	>25	>25	12.08 (34.12)	
(–)-Isovallesiachotamine (**53**)	3.94 (11.73)	5.01 (14.91)	3.16 (9.40)	
Tubotaiwine *N*-oxide (**58**)	>25	>25	>25	
N(4)-Chloromethyltubotaiwine chloride (**59**)	>25	>25	>25	
Alkaloids from *K. pauciflora* (stem-bark)				
Compound **63**	>25	>25	>25	
Compound **64**	>25	>25	18.13 (58.48)	
11,12-Dimethoxykopsinaline (**77**)	>25	>25	>25	
Alkaloids from *K. pauciflora* (leaves)				
Compound **62**	>25	>25	10.80 (30.51)	
Compound **63**	>25	>25	>25	
Larutenine (**65**)	>25	>25	4.63 (15.75)	
Compound **70**	>25	>25	2.75 (7.81)	
(–)-Catharinensine (**72**)	2.77 (7.82)	2.42 (6.84)	0.05 (0.14)	
Tetrahydroalstonine pseudoindoxyl (**73**)	>25	>25	>25	
Andransinine (**90**)	>25	>25	1.61 (4.24)	
Compound **91**	>25	>25	8.06 (22.02)	
Stemmadenine (**94**)	>25	>25	>25	
Alkaloids from *Penicillium* sp. (CDA p48.3)				
Variotin (**104**)	>25	>25	>25	
Control				
Vincristine	1.4 ng/mL (1.70 nM)	0.8 μg/mL (0.97 μM)		1.8 ng/mL (2.18 nM)
Verapamil	>1.0 (> 2.20)	>1.0 (> 2.2)		0.33 (0.73)

[a] With added vincristine 0.1 μg/mL, which did not affect the growth of the KB/VJ300 cells.

Chapter Three

3 Experimental

3.1 Source and Authentication of Plant and Fungi Samples

The plant materials were collected from various locations in Malaysia and were identified by Dr. Richard C. K. Chung (Forest Research Institute, Malaysia). All plant materials were screened for their alkaloidal constituents before any chemical analysis was carried out. Voucher specimens are deposited at the Herbarium, University of Malaya (UM). The details are given in Table 3.1.

Table 3.1: Source and Authentication of Plant Materials

Herbarium Specimen No.	Locality	Species	Date of Collection	Herbarium
K 672	Pahang	*L. griffithii*	Sept 2005	University of Malaya
K 678	Terengganu	*K. pauciflora*	May 2008	University of Malaya

The fungi samples were collected by Professor Dr. Noorlidah Abdullah (Biotechnology), from the Institute of Biological Sciences, University of Malaya. The only alkaloid producing strain was labelled as *Penicillium* sp. (CDA p48.3).

3.2 General

Melting points were determined on Mel-Temp melting point apparatus and were uncorrected. Optical rotations were determined on a Jasco P-1020 digital polarimeter. UV spectra were obtained on a Shimadzu UV-3101PC spectrophotometer. IR spectra were recorded on a Perkin-Elmer 1600 Series or a Perkin-Elmer RX1 FT-IR spectrophotometer.

ESIMS and HRESIMS were obtained on an Agilent 6530 Q-TOF mass spectrometer. HREIMS and HRLSIMS were obtained at Organic Mass Spectrometry, Central Science Laboratory, University of Tasmania, Tasmania, Australia.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a JEOL JNM-LA 400 and JNM-ECA 400 spectrometers at 400 and 100 MHz, respectively. Coupling constants (J) are reported in Hz and δ in ppm.

X-ray diffraction analysis was carried out on a Bruker SMART APEX II CCD area detector system equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (λ = 0.71073 Å), at 100K, or, on an Agilent Technologies SuperNova Dual CCD area detector system equipped with mirror monochromator and a SuperNova (Cu K_α) X-ray source (λ=1.50352 Å). The structure was solved by direct methods (SHELXS-97) and refined with full-matrix least-squares on F^2 (SHELXL-97). I thank Mr. Low Yun Yee and Professor Ward Robinson for carrying out X-ray diffraction analyses.

All solvents were distilled prior to use with the exception of diethyl ether, which was passed through activated neutral alumina before use.

3.3 Chromatographic Methods

3.3.1 Column Chromatography

Flash chromatography was performed using Merck silica gel 9385 (230-400 Mesh ASTM). The ratio of silica gel to the sample was approximately 30:1 for crude samples and 100:1 for semi-pure fractions. The gel was made into a slurry with chloroform before it was packed onto the column and was allowed to equilibrate for at least an hour before use. When diethyl ether was used as an eluting solvent, the column was packed by the dry packing method. The solvent systems normally used as eluents were chloroform with increasing methanol gradient or diethyl ether with increasing ethyl acetate gradient. Fractions were monitored by thin layer chromatography (TLC) and appropriate fractions were combined and where necessary subjected to further separation by re-chromatography or preparative centrifugal TLC.

3.3.2 Sephadex LH-20

The dried powder of Sephadex LH-20 was allowed to swell in methanol for at least 3 hours before use. The slurry was poured onto the column and allowed to equilibrate to room temperature. The sample was filtered with a 0.45 μm nylon membrane before it was loaded into the column to ensure a longer column life. The column can be re-generated by washing of the Sephadex LH-20 gel with 2–3 column volumes of eluent, followed by re-equilibration.

3.3.3 High Performance Liquid Chromatography (HPLC)

High performance liquid chromatography (HPLC) was use for the separation of fungi and bacteria samples. The instruments were: Waters 600 (analytical and semi-preparative HPLC) and Waters Autopurification System (semi- and preparative HPLC). Several C18 reverse phase HPLC columns of different dimensions were use during this study, including, a Merck Chromolith semi-preparative column (10 x 100 mm), Waters X-Bridge (4.6 x 50 mm), and the Waters RCM-100 radial compression module. All samples were filtered with 0.45 μm nylon membrane before use. The solvent systems normally used as eluents were acetonitrile, methanol, and water.

3.3.4 Thin Layer Chromatography (TLC)

Thin layer chromatography (TLC) was routinely used to detect and separate the various alkaloids. The crude alkaloidal extracts, fractions from chromatography, and isolated pure alkaloids were examined by TLC using pre-coated 5 x 10 cm aluminium plates, 0.25 mm thickness, silica gel 60 F_{254} (Merck, Darmstadt, G.F.R.). The TLC plates were spotted with a piece of fine glass capillary tube and then developed in saturated chromatographic tanks with various solvent systems at room temperature. The alkaloidal spots were visualized by examination of the TLC plates under UV light (254 nm), followed by spraying with Dragendorff's reagent, which formed orange spots. The hR_f values of the alkaloids are tabulated in Table 3.2.

Table 3.2: The hR_f Values of Alkaloids Isolated from *Leuconotis griffithii*, *Kopsia pauciflora*, and *Penicillium* sp. (CDA p48.3)

Alkaloid	$CHCl_3$	EtOAc	Et_2O	$CHCl_3$/MeOH (10:1)	EtOAc/MeOH (20:1)
Leucolusine (**1**)	14	53	40	80	56
Leuconicine A (**2**)	6	4	0	66	7
Leuconicine B (**3**)	9	3	0	76	6
Leuconicine C (**4**)	20	37	16	84	48
Leuconicine D (**5**)	35	41	24	88	48
Leuconicine E (**6**)	27	41	18	84	42
Leuconicine F (**7**)	0	0	0	22	0
Leuconicine G (**8**)	0	0	0	22	0
Leuconodine A (**9**)	14	49	22	73	52
Leuconodine B (**10**)	8	51	21	69	54
Leuconodine C (**11**)	4	30	3	55	40
Leuconodine D (**12**)	35	62	66	81	62
Leuconodine E (**13**)	22	63	61	74	60
Leuconoxine (**14**)	22	63	25	77	49
Leuconodine F (**15**)	38	55	24	82	58
Mersicarpine (**16**)	7	65	75	70	70
Arboloscine (**17**)	35	65	79	81	70
3,14-Dehydroleuconolam (**18**)	0	33	6	69	41
Leuconolam (**19**)	0	16	2	63	27
O-Methylleuconolam (**20**)	43	67	53	79	66
6,7-Dehydroleuconoxine (**21a**)	42	58	43	96	51
Nor-rhazinicine (**22**)	14	54	33	94	53
5,21-Dihydrorhazinilam *N*-oxide (**23**)	0	0	0	12	0
5,21-Dihydrorhazinilam (**24**)	3	12	9	43	24
Rhazinilam (**25**)	14	57	40	74	61
Rhazinal (**26**)	11	42	20	94	49
Rhazinicine (**27**)	11	51	29	70	55
Eburnamaline (**28**)	0	12	9	54	23
(+)-Eburnamonine (**29**)	18	24	35	79	26
(+)-Eburnamenine (**30**)	9	31	39	77	36
O-Methylisoeburnamine (**31**)	5	24	24	67	29
O-Methyleburnamine (**32**)	10	28	31	76	34
(+)-Isoeburnamine (**33**)	0	14	12	49	25
(–)-Eburnamine (**34**)	4	21	18	51	29
(±)-Vincamine (**35**)	5	21	14	70	30
Leucophyllidine (**36**)	4	9	3	50	22
Leuconoline (**37**)	0	5	2	29	11
Leucofoline (**38**)	0	2	1	33	4
Leucoridine A (**39**)	2	1	0	26	4
Leucoridine B (**40**)	4	4	3	40	5
Leucoridine C (**41**)	0	2	0	26	2
Leucoridine D (**42**)	2	2	2	37	4
Tetrahydroalstonine (**43**)	22	76	73	84	76
17(*S*)-Ajmalicinial (**44**) and 17(*R*)-ajmalicinial (**45**)	0	27	14	36	37
Akuammidine (**46**)	3	38	26	50	53
16(*R*)-19,20-*E*-Isositsirikine (**47**)	3	12	9	43	24
16(*S*)-19,20-*E*-Isositsirikine (**48**)	0	9	6	30	17
Z-Geissoschizol (**49**)	0	19	6	27	29

Table 3.2, continued

Alkaloid	$CHCl_3$	EtOAc	Et_2O	$CHCl_3$/MeOH (10:1)	EtOAc/MeOH (20:1)
Fluorocarpamine (**50**)	6	15	10	54	24
Pleiocarpamine (**51**)	6	17	13	43	6
16-Hydroxymethylpleiocarpamine (**52**)	0	24	3	31	35
(–)-Isovallesiachotamine (**53**)	5	65	45	75	62
(–)-Isovallesiachotamine (**53**) and (+)-vallesiachotamine (**54**)	6	66	45	72	65
Norfluorocurarine (**55**)	4	4	3	49	8
12-Hydroxynorfluorocurarine (**56**)	0	3	1	32	4
Tubotaiwine (**57**)	0	5	4	46	5
Tubotaiwine *N*-oxide (**58**)	0	3	0	29	3
N(4)-Chloromethyltubotaiwine chloride (**59**)	0	0	0	15	1
Venoterpine (**60**)	0	20	10	42	25
Syringaresinol (**61**)	5	55	19	73	52
Compound **62**	15	59	72	79	55
Compound **63**	9	33	47	73	38
Compound **64**	22	59	71	79	61
Larutenine (**65**)	9	25	31	70	31
(+)-19-Oxoeburnamine (**66**)	1	20	10	44	33
(–)-19(*R*)-Hydroxyisoeburnamine (**67**)	0	0	0	36	14
(+)-19(*R*)-Hydroxyeburnamine (**68**)	0	0	0	37	14
Compound **69**	39	76	69	98	80
Compound **70**	4	63	52	77	61
Compound **71**	0	23	0	45	30
(–)-Catharinensine (**72**)	8	65	61	72	60
Tetrahydroalstonine pseudoindoxyl (**73**)	5	62	51	81	63
(+)-Aspidospermidine (**74**)	5	30	35	55	34
(+)-1,2-Dehydroaspidospermidine (**75**)	7	31	33	75	37
(–)-Quebrachamine (**76**)	5	61	72	52	56
11,12-Dimethoxykopsinaline (**77**)	1	12	6	41	22
Pseudokopsinine (**78**)	4	8	6	41	13
Kopsinine (**79**)	17	57	60	52	34
Kopsamine (**80**)	26	72	48	75	59
N(1)-Decarbomethoxykopsamine (**81**)	5	33	28	52	45
Kopsilongine (**82**)	18	50	46	76	59
Paucifinine (**83**)	5	33	44	73	49
Kopsanone (**84**)	24	40	32	74	45
11,12-Methylenedioxykopsine (**85**)	23	54	35	75	56
12-Methoxykopsine (**86**)	5	13	4	64	24
Kopsifine (**87**)	8	73	30	63	73
N(1)-Decarbomethoxykopsifine (**88**)	2	45	7	49	67
Akuammicine (**89**)	2	11	12	58	35
Andransinine (**90**)	4	16	16	42	23
Compound **91**	2	15	8	35	21
Condylocarpine (**92**)	10	13	7	65	21
Precondylocarpine (**93**)	8	6	6	39	10
Stemmadenine (**94**)	0	3	1	25	4
Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (**95**)	34	53	48	68	68
Methyl 11,12-methylenedioxychanofruticosinate (**96**)	28	66	49	79	70

Table 3.2, continued

Alkaloid	$CHCl_3$	EtOAc	Et_2O	$CHCl_3$/MeOH (10:1)	EtOAc/MeOH (20:1)
Methyl chanofruticosinate (**97**)	36	86	82	94	90
Methyl *N*(1)-decarbomethoxychanofruticosinate (**98**)	32	63	52	76	66
Methyl 12-methoxychanofruticosinate (**99**)	34	61	35	74	63
(–)-Norpleiomutine (**100**)	4	8	6	44	9
Compound **101**	–	–	–	54	–
Compound **102**	–	–	–	67	–
Compound **103**	–	–	–	54	–
Variotin (**104**)	–	–	–	72	–
Viriditin (**105**)	–	–	–	38	–
cyclo (L-Phenylalanine-*trans*-4-hydroxy-L-proline) (**106**)	–	–	–	32	–
cyclo (L-Leucine-*trans*-4-hydroxy-L-proline) (**107**)	–	–	–	20	–

3.3.5 Preparative Centrifugal TLC

Preparative centrifugal TLC was carried out using a round chromatographic plate measuring 24 cm in diameter. To prepare the chromatographic plate, the edge of the plate is secured with cellophane tape to form a mould. Silica gel (Merck 7749, 50 g) is added to about 110 ml of cold distilled water to give a slurry. The slurry is shaken and is then quickly poured onto the circular glass plate before setting commences. The circular glass plate is rotated while the gel is being poured to obtain an even setting. The plate is then left to air-dry for about an hour before being dried in an oven at 80 ℃ for about 12 hours. The sample was dissolved in a minimum volume of a suitable solvent and loaded at the centre of the plate while the plate is spinning to form a thin band. Elution is then carried with the appropriate solvent system. The fractions are collected, concentrated by rotary-evaporation, examined by TLC, and combined where appropriate. Some of the solvent systems used as eluents were:

1. Chloroform

2. Chloroform: Hexanes

3. Chloroform with added 1% of liquid ammonia

4. Chloroform: Methanol

5. Diethyl ether

6. Diethyl ether: Hexanes

7. Diethyl ether: Methanol

8. Diethyl ether with added 1% of liquid ammonia

9. Ethyl acetate

10. Ethyl acetate: Hexanes

11. Ethyl acetate: Methanol

12. Ethyl acetate with added 1% of liquid ammonia

13. Acetone: Hexanes

3.4 Spray Reagent (Dragendorff's Reagent)

Solution A: 0.85 g of bismuth nitrate was dissolved in a mixture of 10 mL glacial acetic acid and 40 mL of distilled water.

Solution B: 8 g of potassium iodide was dissolved in 20 mL of distilled water.

A stock solution was prepared by mixing equal volumes of solutions A and B.

Dragendorff”s reagent was prepared by mixing 1 mL of stock solution with 2 mL of glacial acetic acid and 10 mL of distilled water. Orange spots on the developed TLC plates indicate the presence of alkaloids.

3.5 Cultivation and Fermentation of Fungi Strains

The pure fungi strain was grown on GYMP (glucose 1.5 %–yeast 0.8 %–malt extract 0.8 %–peptone 0.8 %) agars. Ten plugs of 7 days old culture were cut from the periphery of the colony and transferred into 100 mL sterile liquid GYMP in 500 mL Erlenmeyer flasks (thirty 500 mL Erlenmeyer flask, containing 100 mL of liquid GYMP each) and incubated under static conditions at 27 ℃ for 14 days.

3.6 Extraction of Alkaloids

3.6.1 Extraction of Alkaloids from Plant

The plant materials were dried and ground before extracting with 95% ethanol for 2–3 days at room temperature. The ethanol extract was filtered and the residue was then re-extracted with a fresh portion of distilled ethanol. This procedure was repeated 5 or 6 times. The combined extract was then concentrated by distillation under reduced pressure using a rotary-evaporator to about a tenth of the original volume. The concentrated extract was then added slowly into 5% hydrochloric acid with constant stirring. The acidic solution was then filtered through kieselguhr to remove the non-

alkaloidal substances. The filtrate was then basified with concentrated ammonia solution to about pH 10 with cooling and the liberated alkaloids were extracted exhaustively with chloroform. The chloroform extract was then washed with distilled water and dried over anhydrous sodium sulfate. Finally, the solvent was removed by evaporation under reduced pressure to furnish the crude alkaloidal mixture.

3.6.2 Extraction of Alkaloids from Fungi

The culture broth was centrifuged, followed by filtration through kieselguhr to separate the supernatant and mycelia. The supernatant or the liquid broth was extracted exhaustively with ethyl acetate, followed by washing of the ethyl acetate extract with distilled water and drying over anhydrous sodium sulfate. The solvent was removed under reduced pressure to yield the crude extract. The mycelia were extracted exhaustively with methanol. The methanol extract was dried over anhydrous sodium sulfate, followed by removal of solvent under reduced pressure to furnish the crude mixture.

3.7 Isolation of Alkaloids

3.7.1 General Procedure

The crude mixture obtained from the extraction procedure described above was initially fractionated by vacuum chromatography over silica gel. The column was eluted with

chloroform, followed by a stepwise increase of methanol gradient. Based on TLC, the many fractions collected were pooled into several major fractions, which were then subjected to further fractionation by flash chromatography, vacuum chromatography, HPLC, Sephadex LH-20, or preparative centrifugal TLC until pure compounds are obtained.

3.7.2 Isolation of Alkaloids from *Leuconotis griffithii*

Extraction of 13.8 kg of stem-bark material yielded *ca.* 31 g of crude alkaloidal mixture. This mixture was then subjected to chromatography as summarized in the flow diagram shown in Figure 3.1 to yield 60 pure alkaloids and 1 lignan.

3.7.3 Isolation of Alkaloids from *Kopsia pauciflora*

Extraction of 19 kg of the stem-bark of *K. pauciflora* gave *ca.* 58 g of crude alkaloidal mixture. By utilizing various chromatographic methods, a total of 26 alkaloids were isolated. The flow diagram depicting the isolation of the alkaloids from the stem-bark of *K. pauciflora* is shown in Figure 3.2.

The leaves of the same plant gave 45 g of crude material from the extraction of *ca.* 9 kg of plant material. From this mixture, 35 alkaloids were separated. The isolation of alkaloids from the leaves of *K. pauciflora* is summarized in Figure 3.3.

3.7.4 Isolation of Alkaloids from *Penicillium* sp. (CDA p48.3)

Extraction of 3 L of the liquid broth of *Penicillium* sp. gave *ca.* 0.86 g of crude mixture. From this mixture, a total of 7 alkaloids were isolated. The isolation of alkaloids from the broth extract of *Penicillium* sp. is summarized Figure 3.4.

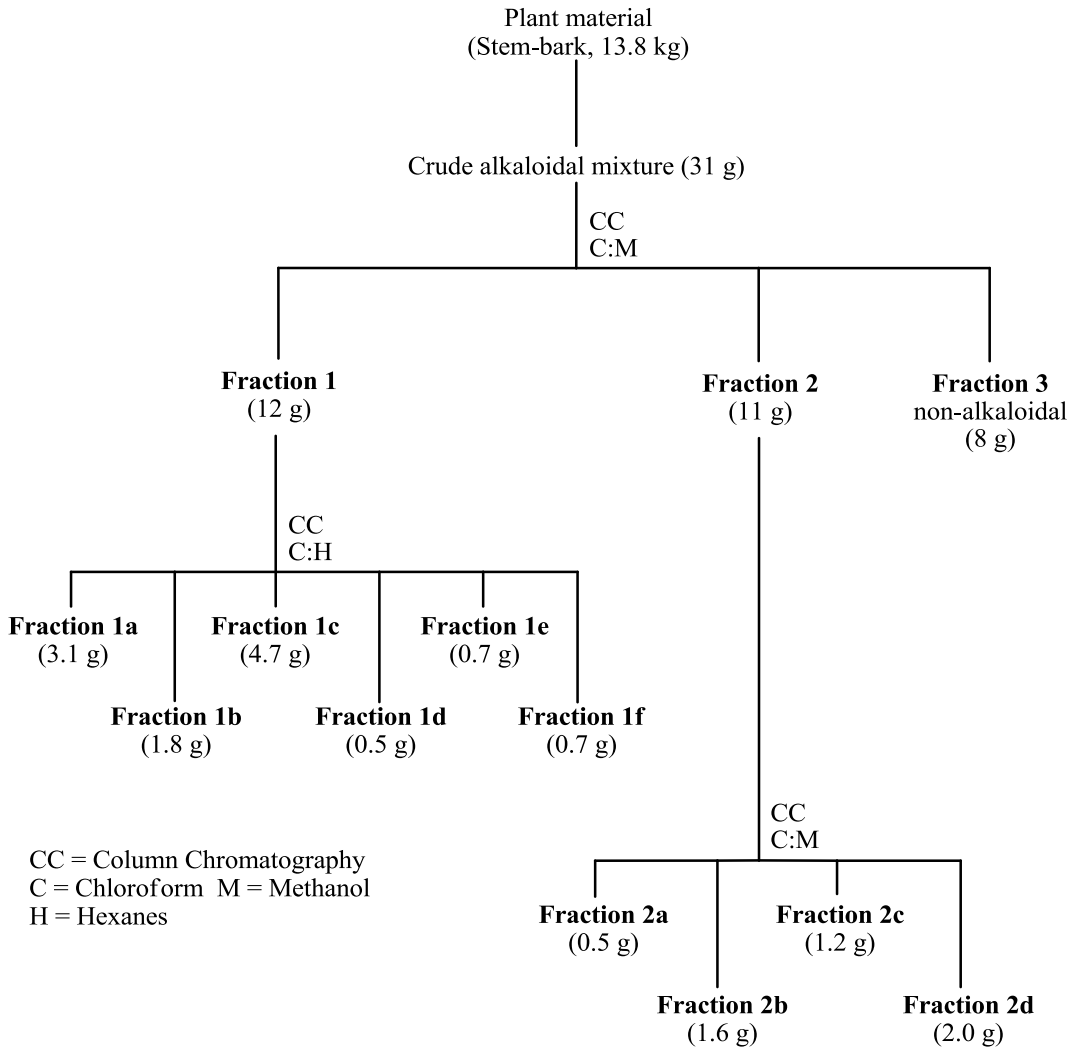


Figure 3.1: Isolation of alkaloids from the stem-bark extract of *Leuconotis griffithii*

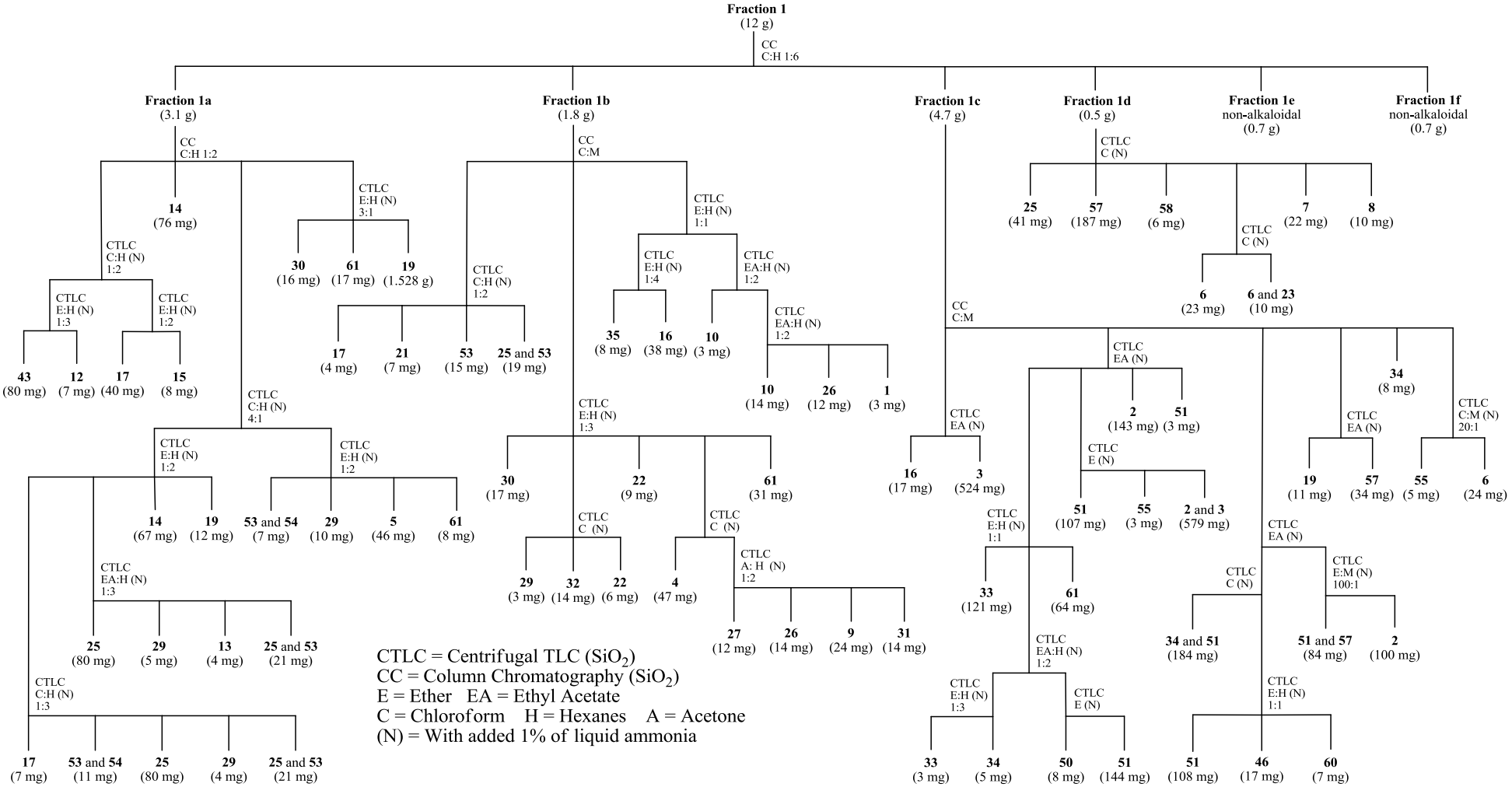
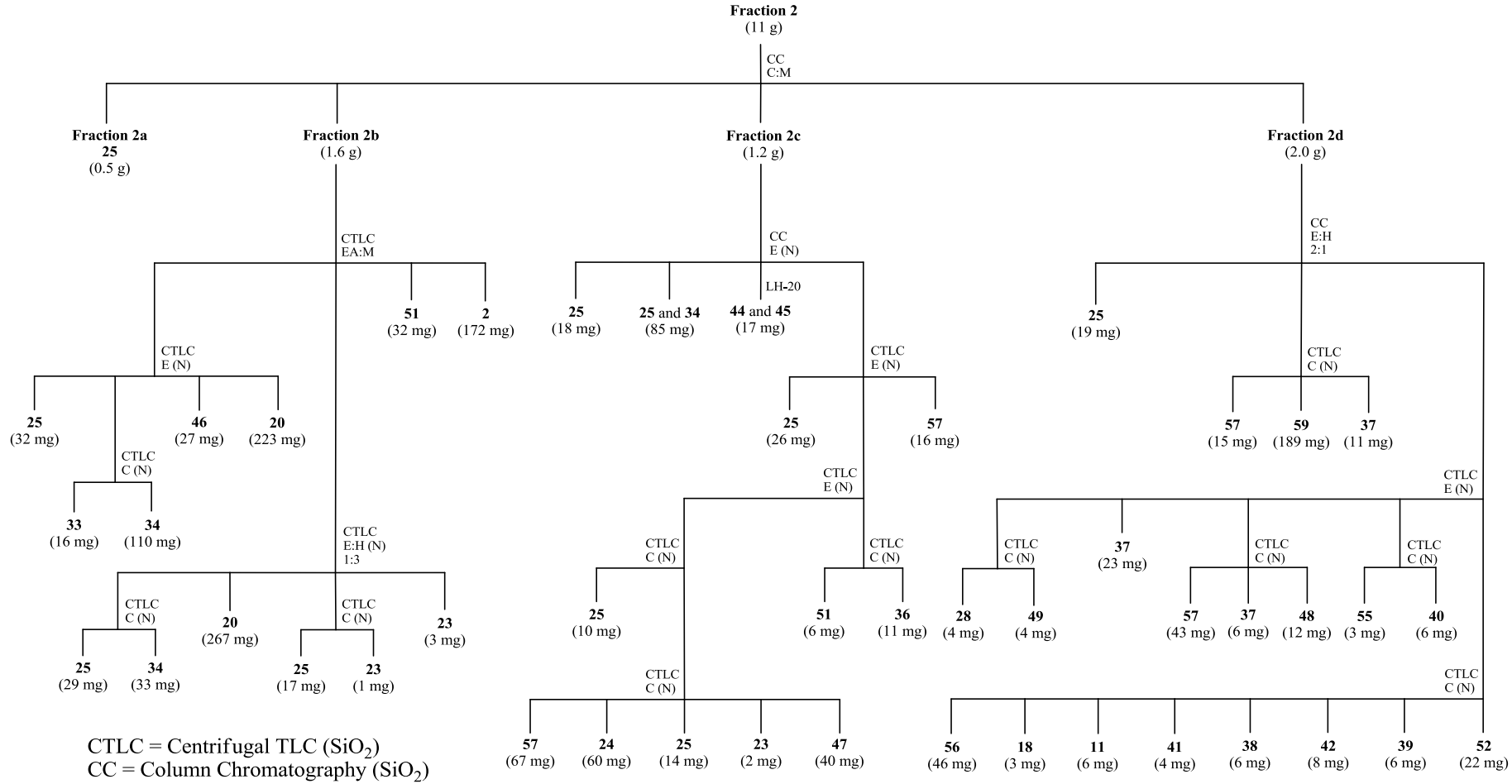


Figure 3.1, continued



CTLC = Centrifugal TLC (SiO_2)
CC = Column Chromatography (SiO_2)
E = Ether EA = Ethyl Acetate
C = Chloroform H = Hexanes
LH-20 = Sephadex LH-20
(N) = With added 1% of liquid ammonia

Figure 3.1, continued

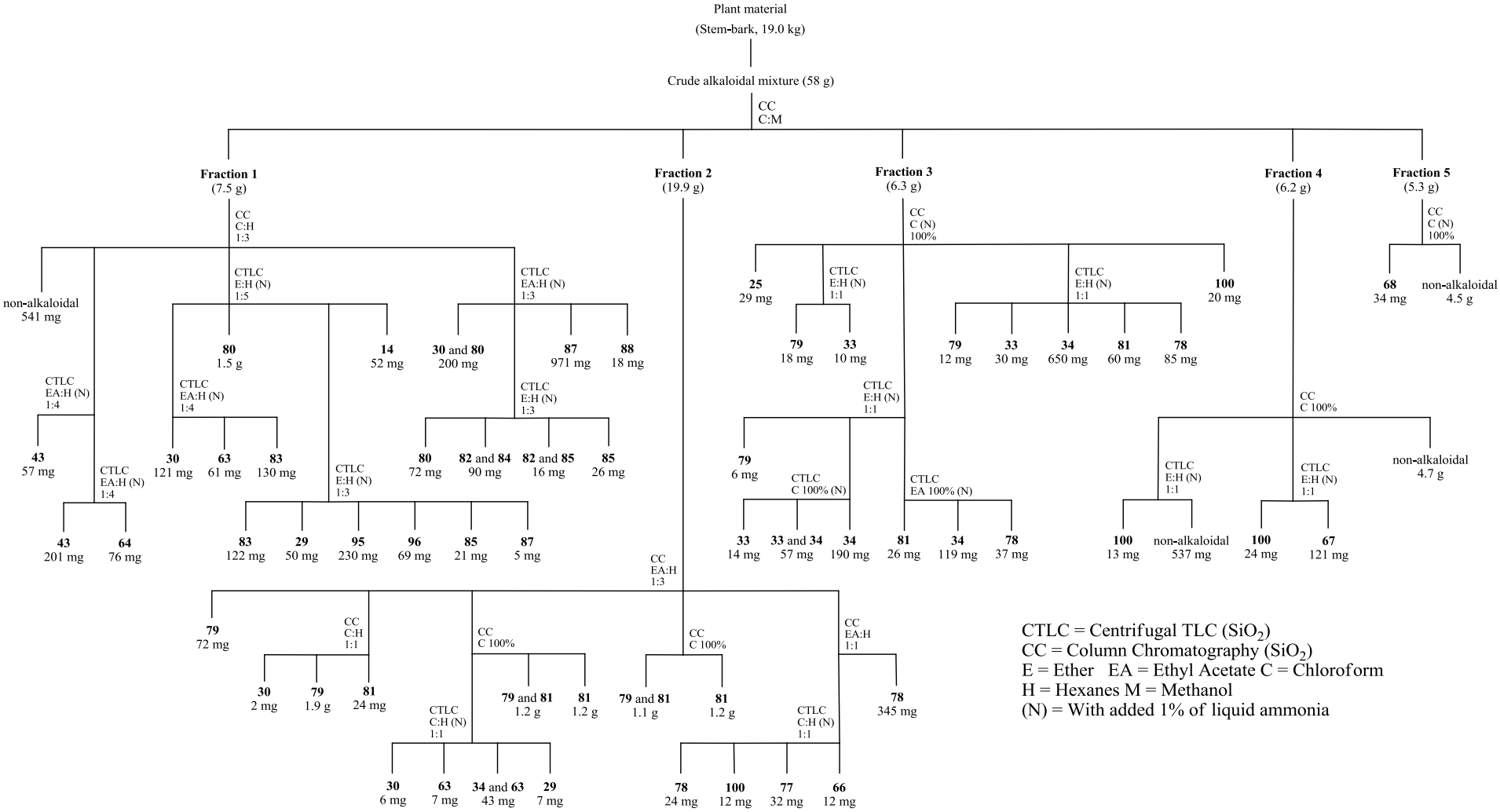


Figure 3.2: Isolation of alkaloids from the stem-bark extract of *Kopsia pauciflora*

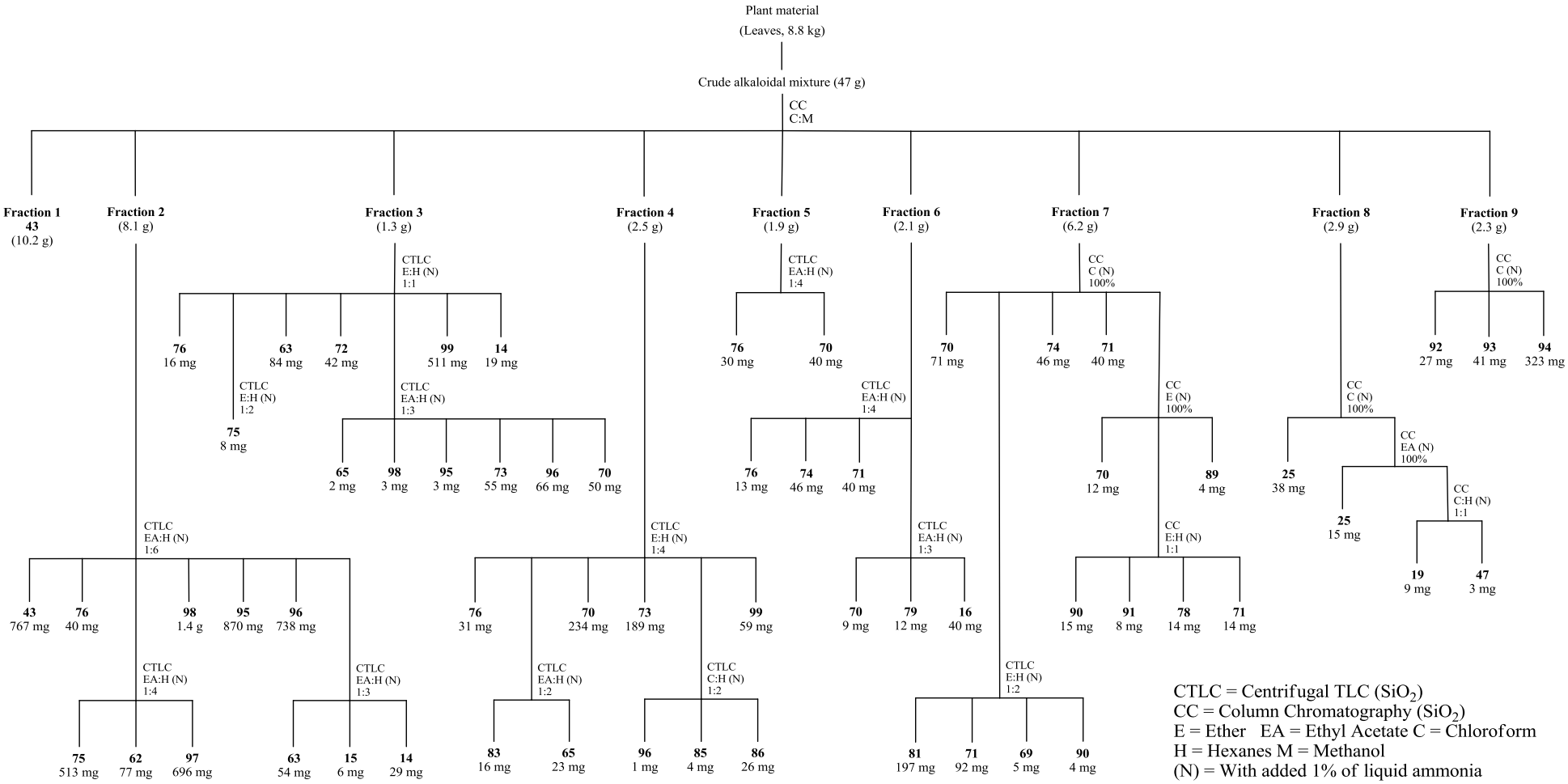
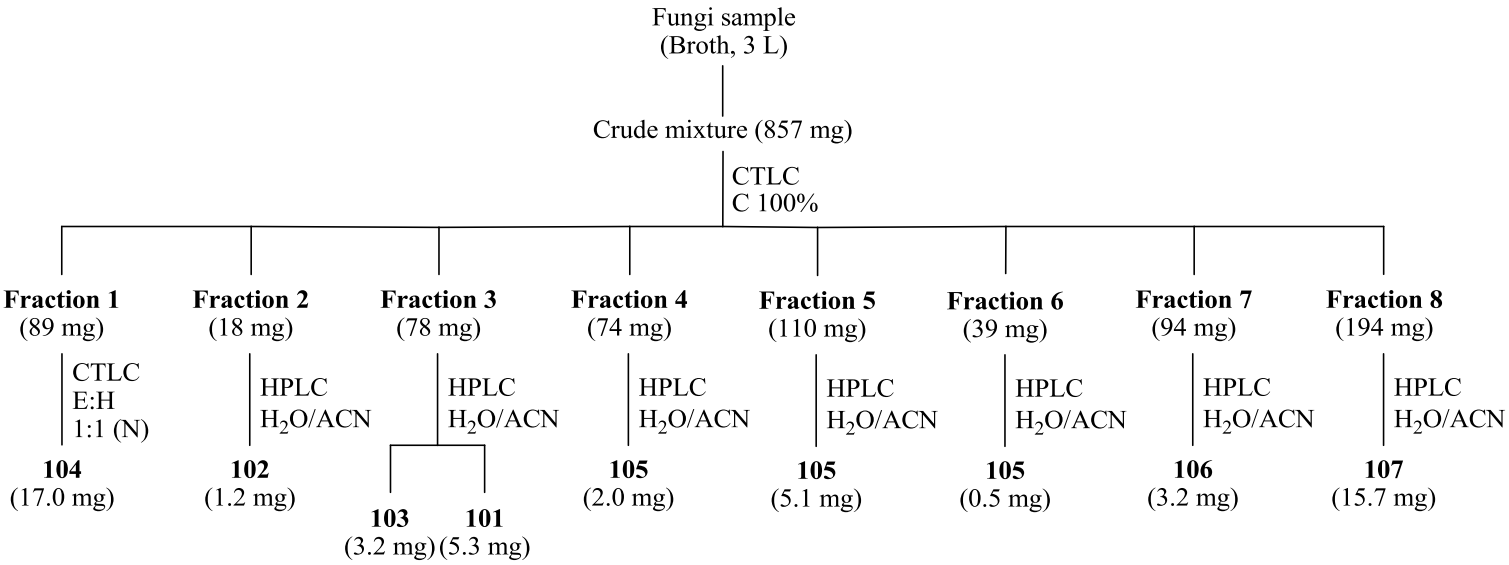


Figure 3.3: Isolation of alkaloids from the leaf extract of *Kopsia pauciflora*



CTLC = Centrifugal TLC (SiO_2)
HPLC = High Performance Liquid CHromatography
E = Ether H = Hexanes C = Chloroform
H_2O = Water ACN = Acetonitrile
(N) = With added 1% of liquid ammonia

Figure 3.4: Isolation of alkaloids from the culture broth extract of *Penicillium* sp. (CDA p48.3)

3.8 Compound Data

Alkaloids from L. griffithii

Leucolusine (1): light yellowish oil; $[\alpha]_D$ +55 (*c* 0.12, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 206 (4.23), 252 (3.60), 288 (2.93) nm; IR (dry film) ν_{max} 3406 (OH), 3254 (NH), 1722 (lactam) cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.2; EIMS *m/z* 330 $[M]^+$ (7), 312 (2), 302 (8), 285 (12), 271 (35), 257 (2), 231 (2), 205 (4), 182 (47), 168 (100), 154 (19), 140 (40), 110 (16), 96 (11), 81 (8), 69 (11), 55 (15); HREIMS *m/z* 330.1942 (calcd for $C_{19}H_{26}N_2O_3$, 330.1943). HMBC: ^2J NH to C(13); H(3) to C(14); H(17) to C(16); H(16) to C(17); H(19) to C(18); H(18) to C(19); H(19) to C(20). ^3J H(6) to C(2); H(15), H(21) to C(3); H(21) to C(5); NH, H(9) to C(7); NH, H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(17), H(19), H(21) to C(15); H(21) to C(16); H(19), H(21) to C(17); H(17), H(21) to C(19); H(14), H(18) to C(20); H(3), H(5), H(15), H(16), H(17), H(19) to C(21). NOE: H(5)/H(21); H(12)/NH; H(18)/H(21); H(21)/H(5), H(18); NH/H(12).

Leuconicine A (2): light yellowish oil; $[\alpha]_D$ −473 (*c* 0.24, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 211 (4.28), 282 (3.55), 369 (3.82) nm; IR (dry film) ν_{max} 3361, 1672, 1614 cm^{-1}; IR ($CHCl_3$ solution) ν_{max} 3684, 3620, 3479, 3299, 1674, 1613 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.3 and 2.4, respectively; EIMS *m/z* 361 $[M]^+$ (100), 344 (8), 332 (13), 316 (7), 288 (18), 277 (33), 260 (44), 246 (63), 218 (17), 204 (40), 190 (28), 166 (7), 135 (4), 123 (68), 94 (22); HREIMS *m/z* 361.1791 (calcd for $C_{22}H_{23}N_3O_2$, 361.1790). HMBC: ^2J H(6) to C(5); H(6) to C(7); H(15) to C(16); H(19) to C(18); H(18) to C(19); H(19), H(21) to C(20); H(20) to C(21); H(17) to C(23); NH to *C*ONH_2.

^{3}J H(3), H(6), H(15), H(17) to C(2); H(5), H(6), H(15), H(21) to C(3); H(3), H(21) to C(5); H(5), H(9), H(14) to C(7); H(3), H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(17), H(19), H(21) to C(15); H(14) to C(16); H(15) to C(17); H(20) to C(18); H(18) to C(20); H(3), H(5), H(15), H(19) to C(21); H(17) to C(22); NH to C(23); H(17) to *C*ONH$_2$. NOESY: H(3)/H(5α), H(9), H(14*R*), H(14*S*); H(5α)/H(3); H(6α)/H(9); H(9)/H(3), H(6α); H(11)/H(12); H(12)/H(11); H(14*R*)/H(3), H(14*S*); H(14*S*)/H(3), H(14*R*), H(20); H(15)/H(17), H(18), H(20); H(17)/H(15), H(18), H(19), NH; H(18)/H(15), H(17), H(20), H(21α); H(19)/H(17); H(20)/H(14*S*), H(15), H(18), H(21α); H(21α)/H(18), H(20); NH/H(17). NOE: H(9)/H(3); H(15)/H(17); H(17)/H(15); H(18)/H(15), H(20).

Leuconicine B (3): light yellowish oil; $[\alpha]_D$ −720 (*c* 1.55, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 203 (4.22), 279 (3.09), 374 (3.76) nm; IR (dry film) ν_{max} 1737, 1703 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.3 and 2.4, respectively; EIMS *m/z* 376 $[M]^+$ (100), 361 (7), 347 (19), 317 (6), 305 (9), 292 (40), 274 (15), 260 (59), 246 (79), 218 (24), 204 (51), 190 (35), 167 (8), 135 (5), 123 (91), 110 (21); HREIMS *m/z* 376.1784 (calcd for $C_{23}H_{24}N_2O_3$, 376.1787). HMBC: ^{2}J H(6) to C(5); H(6) to C(7); H(15) to C(16); H(19) to C(18); H(18) to C(19); H(19), H(21) to C(20); H(20) to C(21); H(17) to C(23). ^{3}J H(3), H(6), H(15), H(17) to C(2); H(5), H(6), H(15), H(21) to C(3); H(3), H(21) to C(5); H(5), H(9), H(14) to C(7); H(3), H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(17), H(19), H(21) to C(15); H(14) to C(16); H(15) to C(17); H(20) to C(18); H(18) to C(20); H(3), H(5), H(15), H(19) to C(21); H(17) to C(22); CO_2*Me*, H(17) to *C*O$_2$Me. NOESY: H(3)/H(5α), H(9), H(14*R*), H(14*S*); H(5α)/H(3); H(6α)/H(9); H(9)/H(3), H(6α); H(11)/H(12); H(12)/H(11); H(14*R*)/H(3), H(14*S*); H(14*S*)/H(3), H(14*R*), H(20);

H(15)/H(17), H(18), H(20); H(17)/H(15), H(18), H(19); H(18)/H(15), H(17), H(20), H(21α); H(19)/H(17); H(20)/H(14*S*), H(15), H(18), H(21α); H(21α)/H(18), H(20). NOE: H(3)/H(5α), H(9), H(14*R*), H(14*S*); H(5α)/H(3), H(5β); H(14*S*)/H(3), H(14*R*), H(15), H(20); H(17)/H(15); H(18)/H(15); H(20)/H(21α); H(21α)/H(20), H(21β); H(21β)/ H(21α).

Leuconicine C (4): light yellowish oil; $[\alpha]_D$ −374 (*c* 0.22, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 205 (4.36), 286 (3.34), 371 (3.84) nm; IR (dry film) ν_{max} 3357, 1674, 1616 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.3 and 2.4, respectively; EIMS *m/z* 359 $[M]^+$ (100), 341 (15), 330 (5), 313 (11), 289 (12), 275 (16), 257 (7), 246 (10), 204 (8), 170 (14), 156 (6), 121 (7); HREIMS *m/z* 359.1629 (calcd for $C_{22}H_{21}N_3O_2$, 359.1634). HMBC: ^2J H(6) to C(5); H(6) to C(7); H(15) to C(16); H(19) to C(18); H(18) to C(19); H(19), H(21) to C(20); H(17) to C(23); NH to *C*ONH$_2$. ^3J H(3), H(6), H(15), H(17) to C(2); H(5), H(6), H(15), H(21) to C(3); H(3), H(21) to C(5); H(5), H(9), H(14) to C(7); H(3), H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(17), H(19), H(21) to C(15); H(14) to C(16); H(15) to C(17); H(18) to C(20); H(3), H(5), H(15), H(19) to C(21); H(17) to C(22); NH to C(23); H(17) to *C*ONH$_2$. NOESY: H(3)/H(5α), H(9), H(14*R*), H(14*S*); H(5α)/H(3); H(6α)/H(9); H(9)/H(3), H(6α); H(11)/H(12); H(12)/H(11); H(14*R*)/H(3), H(14*S*); H(14*S*)/H(3), H(14*R*), H(15)/H(17), H(18); H(17)/H(15), H(18), H(19), NH; H(18)/H(15), H(17), H(21); H(19)/H(17); H(21)/H(18), H(19); NH/H(17).

Catalytic hydrogenation of 4: leuconicine C (**4**) (10.2 mg, 0.028 mmol) was dissolved in CH_2Cl_2 (15 mL) and then stirred over 10% Pd/C (5.8 mg) under a hydrogen

atmosphere at room temperature for 2 h. The catalyst was then removed by filtration over silica gel. Evaporation of the solvent under vacuo, followed by chromatography of the resulting residue (silica gel, MeOH/$CHCl_3$) provided **2** (7.8 mg, 76%).

Leuconicine D (5): light yellowish oil; $[\alpha]_D$ −501 (*c* 0.42, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 211 (4.08), 286 (2.96), 376 (3.72) nm; IR (dry film) ν_{max} 1737, 1698 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.3 and 2.4, respectively; EIMS *m/z* 374 $[M]^+$ (100), 359 (9), 331 (5), 290 (17), 272 (7), 247 (14), 231 (11), 217 (7), 190 (7), 171 (3), 121 (5), 108 (2); HREIMS *m/z* 374.1632 (calcd for $C_{23}H_{22}N_2O_3$, 374.1630). HMBC: ^2J H(6) to C(5); H(6) to C(7); H(15) to C(16); H(19) to C(18); H(18) to C(19); H(19), H(21) to C(20); H(17) to C(23). ^3J H(3), H(6), H(15), H(17) to C(2); H(5), H(6), H(15), H(21) to C(3); H(3), H(21) to C(5); H(5), H(9), H(14) to C(7); H(3), H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(17), H(19), H(21) to C(15); H(14) to C(16); H(15) to C(17); H(18) to C(20); H(3), H(5), H(15), H(19) to C(21); H(17) to C(22); CO_2*Me*, H(17) to *C*O_2Me. NOESY: H(3)/H(5α), H(9), H(14*R*), H(14*S*); H(5α)/H(3); H(6α)/H(9); H(9)/H(3), H(6α); H(11)/H(12); H(12)/H(11); H(14*R*)/H(3), H(14*S*); H(14*S*)/H(3), H(14*R*); H(15)/H(17), H(18); H(17)/H(15), H(18), H(19); H(18)/H(15), H(17), H(21); H(19)/H(17); H(21)/H(18), H(19).

Catalytic hydrogenation of 5: leuconicine D (**5**) (10.5 mg, 0.028 mmol) was dissolved in CH_2Cl_2 (15 mL) and then stirred over 10% Pd/C (5.8 mg) under a hydrogen atmosphere at room temperature for 2 h. The catalyst was then removed by filtration

over silica gel. Evaporation of the solvent under vacuo, followed by chromatography of the resulting residue (silica gel, MeOH/$CHCl_3$) provided **3** (7.5 mg, 71%).

Leuconicine E (6): light yellowish oil; $[\alpha]_D$ −193 (*c* 0.04, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 201 (5.87), 281 (2.81), 365 (3.29) nm; IR (dry film) ν_{max} 3457, 1728 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.5 and 2.6, respectively; EIMS *m/z* 360 $[M]^+$ (100), 345 (4), 316 (29), 287 (25), 259 (12), 232 (29), 217 (13), 204 (22), 191 (13), 163 (4), 121 (10), 108 (7); HREIMS *m/z* 360.1473 (calcd for $C_{22}H_{20}N_2O_3$, 360.1474). HMBC: ^2J H(6) to C(5); H(6) to C(7); H(15) to C(16); H(19) to C(18); H(18) to C(19); H(19), H(21) to C(20); H(17) to C(23). ^3J H(3), H(6), H(15), H(17) to C(2); H(5), H(6), H(15), H(21) to C(3); H(3), H(21) to C(5); H(5), H(9), H(14) to C(7); H(3), H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(17), H(19), H(21) to C(15); H(14) to C(16); H(15) to C(17); H(18) to C(20); H(3), H(5), H(15), H(19) to C(21); H(17) to C(22). NOESY: H(3)/H(5α), H(9), H(14*R*), H(14*S*); H(5α)/H(3); H(6α)/H(9); H(9)/H(3), H(6α); H(11)/H(12); H(12)/H(11); H(14*R*)/H(3), H(14*S*); H(14*S*)/H(3), H(14*R*); H(15)/H(17), H(18); H(17)/H(15), H(18), H(19); H(18)/H(15), H(17), H(21); H(19)/H(17); H(21)/H(18), H(19).

Leuconicine F (7): light yellowish oil; $[\alpha]_D$ −353 (*c* 0.19, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 201 (4.44), 283 (3.39), 367 (3.99) nm; IR (dry film) ν_{max} 3379, 1673, 1618 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.5 and 2.6, respectively; EIMS *m/z* 361 $[M - O]^+$ (100), 344 (7), 332 (12), 316 (7), 289 (15), 277 (30), 260 (33), 246 (50), 232 (11), 204 (21), 190 (15), 167 (4), 123 (34), 110 (10), 94 (8), 69 (7), 41 (5); ESIMS *m/z* 378

$[MH]^+$; HRESIMS *m/z* 378.1825 (calcd for $C_{22}H_{23}N_3O_3$ + H, 378.1812). HMBC: ^2J H(6) to C(5); H(6) to C(7); H(15) to C(16); H(19) to C(18); H(18) to C(19); H(19), H(21) to C(20); H(20) to C(21); H(17) to C(23); NH to *C*ONH$_2$. ^3J H(3), H(6), H(15), H(17) to C(2); H(5), H(6), H(15), H(21) to C(3); H(3), H(21) to C(5); H(5), H(9), H(14) to C(7); H(3), H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(17), H(19), H(21) to C(15); H(14) to C(16); H(15) to C(17); H(20) to C(18); H(18) to C(20); H(3), H(5), H(15), H(19) to C(21); H(17) to C(22); NH to C(23); H(17) to *C*ONH$_2$.

Leuconicine G (8): light yellowish oil; $[\alpha]_D$ –265 (*c* 0.06, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 201 (3.88), 287 (2.79), 367 (3.37) nm; IR (dry film) ν_{max} 1733, 1701 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.5 and 2.6, respectively; EIMS *m/z* 376 $[M - O]^+$ (100), 361 (6), 347 (17), 322 (10), 292 (36), 260 (42), 246 (58), 232 (18), 204 (27), 190 (19), 167 (7), 151 (4), 123 (53), 94 (13), 69 (9), 41 (6); ESIMS *m/z* 393 $[MH]^+$; HRESIMS *m/z* 393.1815 (calcd for $C_{23}H_{24}N_2O_4$ + H, 393.1809). HMBC: ^2J H(6) to C(5); H(6) to C(7); H(15) to C(16); H(19) to C(18); H(18) to C(19); H(19), H(21) to C(20); H(20) to C(21); H(17) to C(23). ^3J H(3), H(6), H(15), H(17) to C(2); H(5), H(6), H(15), H(21) to C(3); H(3), H(21) to C(5); H(5), H(9), H(14) to C(7); H(3), H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(17), H(19), H(21) to C(15); H(14) to C(16); H(15) to C(17); H(20) to C(18); H(18) to C(20); H(3), H(5), H(15), H(19) to C(21); H(17) to C(22); CO_2*Me*, H(17) to *C*O$_2$Me.

Leuconodine A (9): light yellowish oil and subsequently colorless needles from EtOH; mp 135–138 ^{o}C; $[\alpha]_D$ –20 (*c* 0.26, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 242 (3.90), 277 (3.31) nm; IR (dry film) ν_{max} 3346, 1677 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.7 and 2.8; EIMS *m/z*: 326 $[M]^+$ (100), 298 (46), 283 (34), 252 (18), 237 (3), 212 (11), 171 (9), 145 (13), 117 (7); HREIMS $[M]^+$ 326.1633 (calcd for $C_{19}H_{22}N_2O_3$, 326.1630); ESIMS *m/z* 327 $[MH]^+$; HRESIMS *m/z* 327.1699 (calcd for $C_{19}H_{22}N_2O_3$ + H, 327.1703). HMBC: ^{2}J H(16) to C(2); H(14) to C(3); H(7) to C(6); H(6) to C(7); H(7) to C(8); H(12) to C(13); H(14) to C(15); H(17) to C(16); H(16) to C(17); H(19) to C(18); H(15), H(19) to C(20). ^{3}J H(17) to C(2); H(7) to C(5); H(9) to C(7); H(10), H(12) to C(8); H(7), H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(7), H(9), H(11) to C(13); H(3), H(17), H(19) to C(15); H(15), H(19) to C(17); H(15), H(17) to C(19); H(7), H(16), H(18) to C(20); H(3), H(6), H(15), H(17), H(19) to C(21).

Crystallographic data of 9: colorless needles, $C_{19}H_{22}N_2O_3.C_2H_6O$, *M*r = 372.45, orthorhombic, space group $P2_12_12_1$, *a* = 7.3486(4) Å, *b* = 15.0738(7) Å, *c* = 16.6740(8) Å; $\alpha = \beta = \gamma = 90^{o}$, *V* = 1847.0(16) Å^3, *T* = 100 K, *Z* = 4, D_{calc} = 1.339 gcm^{-3}, crystal size 0.04 x 0.17 x 0.63 mm^3, *F*(000) = 800. The final R_1 value is 0.0512 (wR_2 = 0.1263) for 1975 reflections [$I > 2\sigma(I)$].

Leuconodine B (scholarisine G) (10): light yellowish amorphous solid and subsequently colourless block crystals from CH_2Cl_2–MeOH; mp 198–200 ^{o}C; $[\alpha]_D$ –48 (*c* 0.14, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 238 (3.91), 356 (2.93) nm; IR (dry film) ν_{max} 3317, 1674 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.7 and 2.8, respectively; EIMS *m/z* 326 $[M]^+$ (69), 270 (100), 255 (68), 181 (45), 152 (30), 55 (32); HREIMS *m/z*

326.1635 (calcd for $C_{19}H_{22}N_2O_3$, 326.1630). HMBC: ^2J H(16) to C(2); H(6) to C(5); H(6) to C(7); H(17) to C(16); H(16) to C(17); H(19) to C(18); H(18) to C(19); H(17), H(19) to C(20). ^3J H(17) to C(2); H(9) to C(7); H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(17), H(19) to C(15); H(15), H(19) to C(17); H(16), H(18) to C(20); H(6), H(15), H(17) to C(21).

Crystallographic data of 10: colorless block crystals, $C_{19}H_{22}N_2O_3.CH_4O$, *M*r = 358.43, orthorhombic, space group $P2_12_12_1$, a = 8.0382(5) Å, b = 14.5281(9) Å, c = 15.2187(8) Å; $\alpha = \beta = \gamma = 90^o$, V = 1777.24(18) Å^3, T = 100 K, Z = 4, D_{calc} = 1.340 gcm^{-3}, crystal size 0.04 x 0.15 x 0.17 mm^3, F(000) = 768. The final R_1 value is 0.0491 (wR_2 = 0.1091) for 1540 reflections [$I > 2\sigma(I)$].

Leuconodine C (11): light yellowish oil; $[\alpha]_D$ −71 (*c* 0.24, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 201 (3.68), 289 (3.02) nm; IR (dry film) ν_{max} 3286, 1674 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.7 and 2.8, respectively; ESIMS *m/z* 327 $[MH]^+$; HRESIMS *m/z* 327.1710 (calcd for $C_{19}H_{22}N_2O_3$ + H, 327.1703). HMBC: ^2J H(16) to C(2); H(6) to C(5); H(6) to C(7); H(7), H(9) to C(8); H(9) to C(10); H(12) to C(13); H(17) to C(16); H(19) to C(18); H(18) to C(19); H(15), H(17), H(19) to C(20). ^3J H(17) to C(2); H(3), H(7) to C(5); H(9) to C(7); H(6), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(7) to C(13); H(17), H(19) to C(15); H(15), H(19) to C(17); H(16), H(18) to C(20); H(6), H(15), H(17), H(19) to C(21). NOESY: H(6α)/H(9); H(7)/H(19); H(9)/H(6α); H(11)/H(12); H(12)/H(11); H(19)/H(7).

Leuconodine D (12): light yellowish oil and subsequently light yellowish crystals; mp 100–105 ^{o}C; $[\alpha]_D$ –37 (*c* 0.10, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (3.86), 253 (3.68), 283 (3.19), 376 (1.97) nm; IR (dry film) ν_{max} 1670 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.9; EIMS *m/z* 296 $[M]^+$ (15), 268 (45), 253 (100), 151 (15), 136 (7); HREIMS *m/z* 296.1884 (calcd for $C_{19}H_{24}N_2O$, 296.1889). HMBC: ^{2}J H(16) to C(2); H(14) to C(3); H(7) to C(6); H(6) to C(7); H(7) to C(8); H(3) to C(14); H(17) to C(16); H(16) to C(17); H(19) to C(18); H(18) to C(19); H(17), H(19) to C(20). ^{3}J H(17) to C(2); H(5) to C(3); H(3), H(7) to C(5); H(5), H(9) to C(7); H(6) to C(8); H(7), H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(7), H(9), H(11) to C(13); H(17) to C(15); H(15), H(19) to C(17); H(17) to C(19); H(16), H(18) to C(20); H(5), H(6), H(17), H(19) to C(21).

Leuconodine E (13): light yellowish amorphous solid and subsequently colorless crystals from CH_2Cl_2–MeOH; mp >230 ^{o}C; $[\alpha]_D$ –13 (*c* 0.03, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 252 (3.81), 283 (3.37), 318 (2.81), 362 (2.27) nm; IR (dry film) ν_{max} 3416, 1636 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.9; EIMS *m/z* 312 $[M]^+$ (52), 284 (53), 269 (100), 255 (11), 228 (37), 213 (24), 207 (19), 181 (23), 132 (44); HREIMS *m/z* 312.1835 (calcd for $C_{19}H_{24}N_2O_2$, 312.1838). HMBC: ^{2}J H(16) to C(2); H(5) to C(6); H(6) to C(7); H(3) to C(14); H(12) to C(13); H(14) to C(15); H(16) to C(17); H(19) to C(18); H(18) to C(19); H(15), H(19) to C(20). ^{3}J H(17) to C(2); H(3) to C(5); H(5), H(9) to C(7); H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(15), H(19) to C(17); H(14), H(18) to C(20); H(3), H(5), H(6), H(15), H(17) to C(21).

Crystallographic data of 13: colorless flake crystals, $C_{19}H_{24}N_2O_2$, *M*r = 312.40, orthorhombic, space group $P2_12_12_1$, *a* = 8.1326(7) Å, *b* = 10.6116(9) Å, *c* = 18.2366(17) Å; $\alpha = \beta = \gamma = 90^o$, *V* = 1573.80(2) Å^3, *T* = 100 K, *Z* = 4, D_{calc} = 1.318 gcm^{-3}, crystal size 0.03 x 0.17 x 0.80 mm^3, *F*(000) = 672. The final R_1 value is 0.0403 (wR_2 = 0.0966) for 1051 reflections [$I > 2\sigma(I)$].

Leuconoxine (14): colorless oil; $[\alpha]_D$ −71 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (4.42), 244 (3.82), 280 (3.16) nm; IR (dry film) ν_{max} 1695, 1677 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.12 and 2.13, respectively; ESIMS *m*/*z* 311 (MH^+, $C_{19}H_{22}N_2O_2$ + H).

Leuconodine F (6-oxoleuconoxine) (15): colorless oil; $[\alpha]_D$ +75 (*c* 0.03, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 234 (4.12), 251 (4.02), 349 (3.10) nm; IR (dry film) ν_{max} 1715, 1689 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.12 and 2.13, respectively; EIMS *m*/*z* 324 (M^+, $C_{19}H_{20}N_2O_3$).

Mersicarpine (16): colorless oil; $[\alpha]_D$ −18 (*c* 0.28, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 204 (3.96), 239 (4.10), 246 (4.11), 266 (3.85), 275 (3.75), 329 (3.33) nm; IR (dry film) ν_{max} 3318, 1654 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.12 and 2.13, respectively; EIMS *m*/*z* 284 (M^+, $C_{17}H_{20}N_2O_2$).

Arboloscine (17): colorless oil; $[\alpha]_D$ +137 (*c* 0.15, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (3.83), 247 (4.14), 265 (3.99), 321 (3.38) nm; IR (dry film) ν_{max} 3312, 1726, 1662 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.14; LSIMS *m/z* 341 (MH^+, $C_{20}H_{24}N_2O_3$ + H).

3,14-Dehydroleuconolam (18): light yellowish oil; $[\alpha]_D$ −385 (*c* 0.17, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 266 (3.37), 323 (3.01) nm; IR (dry film) ν_{max} 3270, 1694, 1663 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.10; EIMS *m/z* 324 $[M]^+$ (100), 306 (9), 295 (18), 277 (28), 240 (55), 212 (29), 184 (53), 145 (60), 117 (54), 95 (27); HREIMS *m/z* 324.1473 (calcd for $C_{19}H_{20}N_2O_3$, 324.1474). HMBC: ^2J NH, H(16) to C(2); H(14), H(15) to C(3); H(6) to C(5); H(6) to C(7); H(15) to C(14); H(16) to C(17); H(19) to C(18); H(18) to C(19); H(15), H(19) to C(20); OH to C(21). ^3J H(17) to C(2); H(9) to C(7); NH, H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(19) to C(15); NH to C(16); H(15), H(19) to C(17); OH, H(14), H(16), H(18) to C(20); H(3), H(6), H(15), H(17), H(19) to C(21).

Leuconolam (19): light yellowish oil; $[\alpha]_D$ −476 (*c* 0.23, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (4.00), 220 (3.22), 292 (3.96) nm; IR (dry film) ν_{max} 3303, 1682 cm^{-1}; ^1H and ^{13}C NMR data, see Table 2.14; EIMS *m/z* 326 (M^+, $C_{19}H_{22}N_2O_3$).

***O*-Methylleuconolam (20):** light yellowish oil; $[\alpha]_D$ −242 (*c* 0.06, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 238 (3.99), 348 (3.03) nm; IR (dry film) ν_{max} 3477, 1693 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.15; ESIMS *m/z* 341 (MH^+, $C_{20}H_{24}N_2O_3$ + H).

***Epi*-leuconolam (21) or 6,7-dehydroleuconoxine (21a):** light yellowish oil; $[\alpha]_D$ +271 (*c* 0.11, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 202 (4.33), 252 (4.31), 349 (3.68) nm; IR (dry film) ν_{max} 3378, 1691, 1649, 1595 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.15; ESIMS *m*/*z* 309 (MH^+, $C_{19}H_{20}N_2O_2$ + H).

***Nor*-rhazinicine (22):** light yellowish oil and subsequently light yellowish needles from CH_2Cl_2-hexanes; mp 190–192 ^oC; $[\alpha]_D$ –285 (*c* 0.13, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 232 (4.40), 273 (3.61) nm; IR (dry film) ν_{max} 3252, 1752, 1666 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.11; EIMS *m*/*z* 294 $[M]^+$ (82), 265 (60), 237 (100), 223 (15), 209 (24), 195 (29), 182 (25), 167 (20), 154 (15); HREIMS *m/z* 294.1366 (calcd for $C_{18}H_{18}N_2O_2$, 294.1368). HMBC: ^2J H(16) to C(2); H(6) to C(5); H(5) to C(6); H(6) to C(7); H(10), H(12) to C(11); H(15) to C(14); H(17) to C(16); H(16) to C(17); H(19) to C(18); H(18) to C(19); H(15), H(17), H(19) to C(20). ^3J H(17) to C(2); H(5), H(9) to C(7); H(12) to C(8); H(9), H(11) to C(13); H(19) to C(15); H(15), H(19) to C(17); H(15) to C(19); H(18) to C(20); H(5), H(6), H(15), H(17), H(19) to C(21).

Crystallographic data of 22: light yellowish needles, $C_{18}H_{18}N_2O_2$, *M*r = 294.34, monoclinic, space group $P2_1$, *a* = 13.646(3) Å, *b* = 8.3619(17) Å, *c* = 14.658(3) Å; α = = γ = 90°, β = 115.775(11)°, *V* = 1506.2(5) $Å^3$, *T* = 100 K, *Z* = 4, D_{calc} = 1.298 gcm^{-3}, crystal size 0.52 x 0.32 x 0.05 mm^3, *F*(000) = 624. The final R_1 value is 0.1262 (wR_2 = 0.3258) for 7175 reflections [$I > 2\sigma(I)$].

5,21-Dihydrorhazinilam *N*-oxide (23): light yellowish oil; $[\alpha]_D$ –370 (*c* 0.07, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 228 (4.01), 256 (3.35) nm; IR (dry film) ν_{max} 3392, 1655 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.11; EIMS *m/z* 294 $[M - H_2O]^+$ (13), 265 (100), 237 (65), 222 (14), 209 (50), 195 (7), 167 (6), 130 (5); ESIMS *m/z* 313 $[MH]^+$; HRESIMS *m/z* 313.1912 (calcd for $C_{19}H_{24}N_2O_2$ + H, 313.1911). HMBC: ^2J NH, H(16) to C(2); H(6) to C(5); H(5) to C(6); H(6), H(21) to C(7); NH, H(12) to C(13); H(17) to C(16); H(19) to C(18); H(18) to C(19); H(15), H(17), H(21) to C(20). ^3J H(17) to C(2); H(5), H(15) to C(3); H(3), H(21) to C(5); H(21) to C(6); H(5) to C(7); NH, H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(19) to C(15); NH to C(16); H(19), H(21) to C(17); H(15), H(17), H(21) to C(19); H(16), H(18) to C(20); H(3), H(5), H(6), H(19) to C(21). NOE: H(9)/H(21); H(18)/H(19); H(19)/H(18), H(21); H(21)/H(3β), H(9), H(19).

5,21-Dihydrorhazinilam (24): light yellowish oil; $[\alpha]_D$ –296 (*c* 0.19, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 213 (4.31), 227 (4.21), 261 (3.50) nm; ^1H NMR and ^{13}C NMR data, see Table 2.16; EIMS *m/z* 296 (M^+, $C_{19}H_{24}N_2O$).

Rhazinilam (25): colorless prisms ($CHCl_3$-MeOH); mp 204–206 °C; $[\alpha]_D$ –396 (*c* 0.12, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (4.17), 222 (3.86), 270 (3.10) nm; IR (dry film) ν_{max} 3245, 1683 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.16; EIMS *m/z* 294 (M^+, $C_{19}H_{22}N_2O$).

Rhazinal (26): light yellowish oil; $[\alpha]_D$ –187 (*c* 0.19, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 203 (4.55), 234 (3.80), 302 (3.96) nm; ^{1}H NMR and ^{13}C NMR data, see Table 2.17; EIMS *m*/*z* 322 (M^+, $C_{20}H_{22}N_2O_2$).

Rhazinicine (27): light yellowish oil; $[\alpha]_D$ –208 (*c* 0.13, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 207 (4.37), 229 (4.19), 275 (3.65) nm; IR (dry film) ν_{max} 3265, 1666 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.17; EIMS *m*/*z* 308 (M^+, $C_{19}H_{20}N_2O_2$).

(–)-Eburnamaline (28): light yellowish oil; $[\alpha]_D$ –49 (*c* 0.21, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (3.76), 280 (3.16) nm; IR (dry film) ν_{max} 3370 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.18; EIMS *m/z* 312 $[M]^+$ (100), 294 (23), 283 (20), 265 (76), 242 (26), 224 (38), 208 (18), 196 (12), 180 (8), 144 (5); HREIMS *m/z* 312.1827 (calcd for $C_{19}H_{24}N_2O_2$, 312.1838); ESIMS *m/z* 313 $[MH]^+$; HRESIMS *m/z* 313.1926 (calcd for $C_{19}H_{24}N_2O_2$ + H, 313.1911). HMBC: ^2J H(21) to C(2); H(6) to C(5); H(6) to C(7); H(19) to C(18); H(18) to C(19); H(19), H(21) to C(20). ^3J H(6) to C(2); H(5), H(21) to C(3); H(5), H(9), H(21) to C(7); H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(19), H(21) to C(15); H(19) to C(17); H(18) to C(20); H(3), H(5), H(17) to C(21). NOE: H(5α)/H(21); H(5β)/H(21); H(11)/H(12); H(12)/H(11), H(16); H(15α)/H(16); H(15β)/H(17); H(16)/H(12), H(15α), H(17); H(17)/H(15β), H(16), H(18); H(18)/H(17); H(19)/H(21); H(21)/H(5α), H(5β), H(19).

(+)-Eburnamonine (29): colorless oil; $[\alpha]_D$ +82 (*c* 0.05, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 207 (4.42), 245 (4.37), 270 (4.11), 302 (3.80) nm; IR (dry film) ν_{max} 1684 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.19 and 2.20, respectively; ESIMS *m*/*z* 295 (MH^+, $C_{19}H_{22}N_2O$ + H).

(+)-Eburnamenine (30): colorless oil; $[\alpha]_D$ +216 (*c* 0.07, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 223 (3.95), 259 (3.98), 303 (3.42), 310 (3.44), 362 (2.48) nm; ^1H NMR and ^{13}C NMR data, see Tables 2.19 and 2.20, respectively; EIMS *m*/*z* 278 (M^+, $C_{19}H_{22}N_2$).

***O*-Methylisoeburnamine (31):** light yellowish oil; $[\alpha]_D$ +36 (*c* 0.12, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 226 (4.34), 275 (3.76), 289 (3.68) nm; ^1H NMR and ^{13}C NMR data, see Table 2.21; EIMS *m*/*z* 310 (M^+, $C_{20}H_{26}N_2O$).

***O*-Methyleburnamine (32):** light yellowish oil; $[\alpha]_D$ −75 (*c* 0.64, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (4.37), 280 (3.79), 290 (3.70) nm; ^1H NMR and ^{13}C NMR data, see Table 2.21; EIMS *m*/*z* 310 (M^+, $C_{20}H_{26}N_2O$).

(+)-Isoeburnamine (33): light yellow oil; $[\alpha]_D$ +93 (*c* 0.12, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 207 (3.36), 230 (3.92), 283 (3.32), 290 (3.23) nm; IR (dry film) ν_{max} 3315 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.22 and 2.23, respectively; ESIMS *m*/*z* 297 (MH^+, $C_{19}H_{24}N_2O$ + H).

(–)-Eburnamine (34): colorless oil; $[\alpha]_D$ –52 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (4.13), 229 (4.30), 282 (3.79), 292 (3.67) nm; ^{1}H NMR and ^{13}C NMR data, see Tables 2.22 and 2.23, respectively; EIMS *m*/*z* 296 (M^+, $C_{19}H_{24}N_2O$).

(±)-Vincamine (35): light yellowish oil; $[\alpha]_D$ 0 (*c* 0.09, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 232 (3.85), 295 (3.75), 326 (3.91) nm; ^{1}H NMR and ^{13}C NMR data, see Tables 2.22 and 2.23, respectively; ESIMS *m*/*z* 355 (MH^+, $C_{21}H_{26}N_2O_3$ + H).

Leucophyllidine (36): pale yellowish crystals from Et_2O–EtOAc; mp 215–217 ^oC; $[\alpha]_D$ –138 (*c* 0.18, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 230 (4.81), 288 (3.92), 354 (3.97) nm; IR (dry film) ν_{max} 3376 (OH) cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.24; EIMS *m/z* 572 $[M]^+$ (100), 543 (13), 502 (28), 473 (4), 400 (2), 359 (1), 307 (19), 271 (11), 252 (72), 208 (9), 156 (3), 111 (4); HREIMS *m/z* 572.3510 (calcd for $C_{38}H_{44}N_4O$, 572.3515). HMBC: ^2J H(5) to C(6); H(6) to C(7); H(12) to C(11); H(12) to C(13); H(17) to C(16); H(19) to C(18); H(18) to C(19); H(17), H(19) to C(20); H(21') to C(2'); H(6') to C(5'); H(6') to C(7'); H(9') to C(8'); H(3') to C(14'); H(19') to C(18'); H(18') to C(19'); H(17'), H(19'), H(21') to C(20'). ^3J H(3), H(17), H(21) to C(2); H(21) to C(3); H(5), H(9) to C(7); H(12) to C(8); H(12) to C(10); H(9) to C(11); H(9) to C(13); H(16), H(19), H(21) to C(15); H(21) to C(17); H(18) to C(20); H(19) to C(21); H(6') to C(2'); H(5'), H(15'), H(21') to C(3'); H(5'), H(9'), H(21') to C(7'); H(10'), H(12') to C(8'); H(11') to C(9'); H(12') to C(10'); H(9') to C(11'); H(10') to C(12'); H(9'), H(11') to C(13'); H(3'), H(21') to C(15'); H(9) to C(16'); H(19') to C(17'); H(21') to C(19'); H(18') to C(20'); H(5'), H(19') to C(21'). NOE: H(5)/H(6), H(16'); H(16')/H(5); H(18')/H(19').

Crystallographic data of 36: a single crystal of **36** was obtained from Et_2O–EtOAc; $C_{38}H_{44}N_4O$, *M*r = 572.35, monoclinic, space group $P2_1$, *a* = 12.7151(3) Å, *b* = 8.5294(3) Å, *c* = 17.2463(5) Å; *V* = 1770.50(9) $Å^3$, *Z* = 2, D_{calc} = 1.240 g cm^{-3}. The structure was solved by direct methods and refined by the least-square method. The final *R* value is 0.0489.

Leuconoline (37): light yellowish oil and subsequently light yellowish crystals from EtOH; mp 223–224 ^oC; $[\alpha]_D$ +142 (*c* 0.49, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (4.72), 285 (4.21) nm; IR (dry film) ν_{max} 3401, 1713 cm^{-1}; ^1H and ^{13}C NMR data, see Table 2.25; EIMS *m/z* 646 $[M]^+$ (100), 615 (12), 543 (12), 463 (10), 433 (3), 393 (6), 323 (4), 252 (45), 197 (7), 156 (4), 124 (15); HREIMS *m/z* 646.3510 (calcd for $C_{40}H_{46}N_4O_4$, 646.3519). ^2J NH, H(3) to C(2); H(6) to C(5); H(6) to C(7); H(11) to C(10); NH to C(13); H(19) to C(18); H(18) to C(19); H(21') to C(2'); H(6') to C(7'); H(9') to C(8'); H(10') to C(11'); H(14') to C(15'); H(18') to C(19'); H(15'), H(19'), H(21') to C(20'). ^3J H(6), H(14) to C(2); H(21) to C(3); H(3), H(17), H(21) to C(5); NH, H(3), H(5) to C(7); NH, H(12) to C(8); H(11) to C(9); H(12), H(16') to C(10); H(11) to C(13); H(19) to C(15); H(18) to C(20); H(19) to C(21); CO_2Me, H(17) to CO_2Me; H(21') to C(3'); H(9'), H(21') to C(7'); H(10'), H(12') to C(8'); H(11') to C(9'); H(12') to C(10'); H(9') to C(11'); H(10') to C(12'); H(9'), H(11') to C(13'); H(19'), H(21') to C(15'); H(19') to C(17'); H(21') to C(19'); H(14'), H(18') to C(20'); H(5'), H(17'), H(19') to C(21'). NOE: H(11)/H(12); H(12)/NH; NH/H(3), H(12); H(10')/H(9'); H(12')/H(11').

Acetylation of leuconoline (37): to a stirred solution of **37** (9.6 mg, 0.015 mmol), CH_2Cl_2 (2 mL) and 4-(dimethylamino)pyridine (DMAP, 4.5 mg, 0.037 mmol) was

added dropwise acetic anhydride (7 μL, 0.075 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was quenched with 10% Na_2CO_3 (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), the solvent evaporated in vacuo, and the residue purified by preparative centrifugal TLC (SiO_2, Et_2O/hexanes 1:1) to give 7.2 mg (67%) of the diacetate derivative **37a** as light yellowish amorphous solids; mp >224 °C dec; $[\alpha]_D$ +113 (c 0.07, $CHCl_3$); UV (EtOH), λ_{max} (log ε) 210 (4.46), 230 (4.63), 287 (4.08) nm; IR (dry film) ν_{max} 3378, 1746, 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.96 (3H, t, *J* = 7 Hz, Me(18′)), 1.20 (1H, m, H(15′a)), 1.42 (1H, m, H(14′a)), 1.58 (3H, d, *J* = 7 Hz, H(18)), 1.61 (1H, m, H(19′a)), 1.63 (1H, m, H(15′b)), 1.72 (3H, s, COMe), 1.83 (1H, m, H(14′b)), 1.91 (1H, m, H(14a)), 1.98 (3H, s, COMe), 2.14 (1H, m, H(19′b)), 2.23 (1H, m, H(17′a)), 2.46 (1H, m, H(3′a)), 2.50 (1H, m, H(17′b)), 2.59 (1H, m, H(3′b)), 2.62 (1H, m, H(6′a)), 2.63 (1H, m, H(14b)), 2.89 (1H, m, H(5)), 3.01 (1H, m, H(6′b)), 3.03 (3H, s, CO_2Me), 3.14 (1H, m, H(6a)), 3.21 (1H, m, H(15)), 3.29 (1H, td, *J* = 11 and 5 Hz, H(5′a)), 3.38 (1H, dd, *J* = 13.6 and 6.3 Hz, H(5′b)), 3.46 (1H, m, H(6b)), 3.54 (1H, d, *J* = 17 Hz, H(21a)), 3.65 (1H, d, *J* = 17 Hz, H(21b)), 4.04 (1H, s, H(21′)), 4.13 (1H, d, *J* = 10.5 Hz, H(17a)), 4.28 (1H, d, *J* = 10.5 Hz, H(17b)), 4.25 (1H, d, *J* = 12 Hz, H(3)), 5.39 (1H, q, *J* = 7 Hz, H(19)), 5.79 (1H, dd, *J* = 11 and 5.2 Hz, H(16′)), 6.42 (1H, d, *J* = 8 Hz, H(12′)), 6.68 (1H, t, *J* = 7.6 Hz, H(11′)), 6.70 (1H, d, *J* = 9 Hz, H(11)), 6.93 (1H, t, *J* = 7.6 Hz, H(10′)), 7.08 (1H, d, *J* = 9 Hz, H(12)), 7.39 (1H, d, *J* = 7.6 Hz, H(9′)), 8.38 (1H, br s, NH); ESIMS *m/z* 731 $[MH]^+$; HRESIMS *m/z* 731.3813 (calcd for $C_{44}H_{50}N_4O_6$ + H, 731.3803).

Crystallographic data of 37: a single crystal of **37** was obtained from EtOH; $C_{40}H_{46}N_4O_4$, *M*r = 646.81, orthorhombic, space group $P2_12_12_1$, *a* = 7.0778(2) Å, *b* =

13.0650(4) Å, c = 37.7977(12) Å; V = 3495.2(12) Å^3, Z = 4, D_{calc} = 1.229 g cm^{-3}. The structure was solved by direct methods and refined by the least-square method. The final R value is 0.0644 (Rw = 0.1387) for 3119 reflections [$I > 2\sigma(I)$].

Leucofoline (38): light yellowish oil; $[\alpha]_D$ +113 (c 0.28, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 214 (4.26), 273 (3.82) nm; ^{1}H and ^{13}C NMR data, see Table 2.26; ESIMS *m/z* 557 $[MH]^+$; HRESIMS *m/z* 557.3642 (calcd for $C_{38}H_{44}N_4$ + H, 557.3644). HMBC: ^2J H(21) to C(7); H(22'a) to C(16); H(19) to C(18); H(18) to C(19); H(19), H(21) to C(20); H(6') to C(5'); H(21') to C(7'); H(10') to C(11'); H(20') to C(15'); H(22'a) to C(16'); H(19') to C(18'); H(18'), H(20') to C(19'). ^3J H(21) to C(2); H(21) to C(5); H(5), H(9) to C(7); H(10), H(12), H(21) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(21) to C(19); H(18) to C(20); H(3), H(5), H(6), H(19) to C(21); H(22') to C(22); H(6'), H(21'), H(22') to C(2'); H(5'), H(21') to C(3'); H(21') to C(6'); H(9') to C(7'); H(6'), H(10'), H(12'), H(21') to C(8'); H(11') to C(9'); H(12') to C(10'); H(9') to C(11'); H(10') to C(12'); H(9'), H(11') to C(13'); H(18') to C(20'); H(5'), H(19') to C(21'). NOESY: H(9)/H(21); H(18)/H(21); H(19)/H(18), H(20); H(21)/H(9), H(18), H(19), H(20); H(9')/H(10'), H(21'); H(10')/H(9'); H(11')/H(12'); H(12')/H(22a), H(22b), H(11'); H(18')/H(20'); H(19')/H(18'), H(21'); H(20')/H(18'); H(21')/H(9'), H(19'); H(22'a)/H(20), H(12'); H(22'b)/H(12').

Leucoridine A (39): light yellowish oil; $[\alpha]_D$ –29 (c 0.26, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 213 (3.89), 267 (3.52) nm; ^{1}H NMR and ^{13}C NMR data, see Tables 2.27 and 2.28, respectively; ESIMS *m/z* 557 $[MH]^+$; HRESIMS *m/z* 557.3643 (calcd for $C_{38}H_{44}N_4$ + H, 557.3644). HMBC: ^2J H(6) to C(5); H(6) to C(7); H(22) to C(16); H(19)

to C(18); H(18), H(20) to C(19); H(19), H(21) to C(20); H(14') to C(3'); H(6') to C(7'); H(15'), H(22') to C(16'); H(19') to C(18'); H(18') to C(19'); H(21') to C(20'). ^{3}J H(3), H(22), H(22') to C(2); H(15), H(21) to C(3); H(5), H(9), H(14) to C(7); H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(19), H(21), H(22') to C(15); H(15), H(21) to C(19); H(14), H(18) to C(20); H(3), H(5), H(19) to C(21); H(22), H(6'), H(15'), H(22') to C(2'); H(5'), H(6'), H(15'), H(21') to C(3'); H(5'), H(9') to C(7'); H(3'), H(6'), H(10'), H(12') to C(8'); H(11') to C(9'); H(12') to C(10'); H(9') to C(11'); H(10') to C(12'); H(9'), H(11') to C(13'); H(3'), H(21') to C(15'); H(20') to C(18'); H(18') to C(20'); H(3') to C(21'); H(22) to C(22'). NOESY: H(3)/H(5α), H(9), H(14*R*), H(14*S*); H(5α)/H(3); H(9)/H(3), H(6α); H(14*R*)/H(3); H(14*S*)/H(3); H(15)/H(18); H(18)/H(15), H(20); H(19)/H(22b); H(20)/H(18); H(22a)/H(12'); H(22b)/H(19); H(3')/H(9'); H(9')/H(3'); H(12')/H(22a); H(15')/H(18'); H(18')/H(15'). NOE: H(3)/H(5α), H(9), H(14*R*), H(14*S*); H(14*S*)/H(14*R*); H(21β)/H(21α); H(22a)/H(22b), H(12'); H(3')/H(9'), H(21'α); H(5'β)/H(5'α); H(12')/H(22a), H(11'); H(14'*S*)/H(14'*R*), H(21'α); H(15')/H(14'*R*), H(18'), H(20'), H(22'b); H(22'a)/H(22'b); H(22'b)/H(22'a).

Leucoridine B (40): light yellowish oil; $[\alpha]_D$ +56 (*c* 0.29, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 215 (4.45), 268 (4.06), 329 (3.50) nm; ^{1}H NMR and ^{13}C NMR data, see Tables 2.27 and 2.28, respectively; ESIMS *m*/*z* 555 $[MH]^+$; HRESIMS *m*/*z* 555.3487 (calcd for $C_{38}H_{42}N_4$ + H, 555.3488). HMBC: ^{2}J H(6) to C(5); H(6) to C(7); H(22) to C(16); H(19) to C(18); H(18) to C(19); H(19), H(21) to C(20); H(14') to C(3'); H(6') to C(7'); H(15'), H(22') to C(16'); H(19') to C(18'); H(18') to C(19'); H(21') to C(20'). ^{3}J H(3), H(22), H(22') to C(2); H(5), H(15), H(21) to C(3); H(21) to C(5); H(5), H(9), H(14) to C(7); H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to

C(12); H(9), H(11) to C(13); H(3), H(19), H(21), H(22') to C(15); H(15), H(21) to C(19); H(18) to C(20); H(3), H(5), H(19) to C(21); H(22), H(6'), H(15'), H(22') to C(2'); H(5'), H(6'), H(15'), H(21') to C(3'); H(5'), H(9') to C(7'); H(3'), H(6'), H(10'), H(12') to C(8'); H(11') to C(9'); H(12') to C(10'); H(9') to C(11'); H(10') to C(12'); H(9'), H(11') to C(13'); H(3'), H(21') to C(15'); H(18') to C(20'); H(3') to C(21'); H(22) to C(22'). NOESY: H(5α)/H(21); H(21)/H(5α); H(22a)/H(22b); H(22b)/H(22a); H(3')/H(9'); H(9')/H(3').

Leucoridine C (41): light yellowish oil; $[\alpha]_D$ –61 (*c* 0.26, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 206 (4.58), 250 (4.04), 275 (4.02) nm; IR (dry film) ν_{max} 3414, 3358, 1686 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.27 and 2.28, respectively; ESIMS *m*/*z* 575 $[MH]^+$; HRESIMS *m*/*z* 575.3751 (calcd for $C_{38}H_{46}N_4O$ + H, 575.3750). HMBC: ^2J H(6) to C(5); H(6) to C(7); H(22) to C(16); H(18), H(20) to C(19); H(21) to C(20); H(14') to C(3'); H(6') to C(7'); H(15'), H(22') to C(16'); H(19') to C(18'); H(18') to C(19'); H(19'), H(21') to C(20'). ^3J H(3), H(22), H(22') to C(2); H(15), H(21) to C(3); H(5), H(9), H(14) to C(7); NH, H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); NH, H(10) to C(12); H(9), H(11) to C(13); H(3), H(21), H(22') to C(15); H(15), H(21) to C(19); H(18) to C(20); H(3), H(5) to C(21); H(22), H(6'), H(15'), H(22') to C(2'); H(5'), H(6'), H(15'), H(21') to C(3'); H(5'), H(9') to C(7'); H(3'), H(6'), H(10'), H(12') to C(8'); H(11') to C(9'); H(12') to C(10'); H(9') to C(11'); H(10') to C(12'); H(9'), H(11') to C(13'); H(3'), H(19'), H(21') to C(15'); H(20') to C(18'); H(18') to C(20'); H(3'), H(19') to C(21'); H(22) to C(22'). NOESY: H(6α)/H(6β); H(6β)/H(6α); H(14*R*)/H(14*S*), H(15), H(22'b); H(14*S*)/H(14*R*); H(15)/H(14*R*); H(21α)/H(21β); H(21β)/H(21α); H(22a)/H(22b); H(22b)/H(22a); H(18')/H(19'); H(19')/H(18'); H(22'a)/H(22'b); H(22'b)/H(22'a).

Leucoridine D (42): light yellowish oil; $[\alpha]_D$ +6 (*c* 0.40, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 213 (3.70), 253 (3.20), 299 (2.84) nm; IR (dry film) ν_{max} 3246 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.27 and 2.28, respectively; ESIMS *m*/*z* 559 $[MH]^+$; HRESIMS *m*/*z* 559.3794 (calcd for $C_{38}H_{46}N_4$ + H, 559.3795). HMBC: ^2J H(16) to C(2); H(6) to C(7); H(16) to C(15); H(22) to C(16); H(19) to C(18); H(18) to C(19); H(19) to C(20); H(2'), H(6') to C(7'); H(10') to C(11'); H(15'), H(22') to C(16'); H(19') to C(18'); H(18') to C(19'); H(15'), H(19'), H(21') to C(20'). ^3J H(3), H(6), H(22) to C(2); H(5), H(6) to C(3); H(5), H(9), H(14) to C(7); H(3), H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(21) to C(15); H(21) to C(19); H(18) to C(20); H(3), H(5), (19) to C(21); H(11') to C(22); H(6'), H(22') to C(2'); H(2') to C(3'); H(21') to C(5'); H(2') to C(6'); NH', H(5'), H(9') to C(7'); NH', H(3'), H(6'), H(10') to C(8'); H(11') to C(9'); H(22), H(9') to C(11'); H(16), H(10') to C(12'); H(22), H(9'), H(11') to C(13'); H(2'), H(3'), H(21'), H(22') to C(15'); H(15') to C(18'); H(14'), H(18') to C(20'); H(3'), H(5'), H(19') to C(21'); H(2'), H(15') to C(22'). NOESY: H(3)/H(9), H(14*R*), H(14*S*); H(9)/H(3); H(12)/H(22'a); H(14*R*)/H(3); H(14*S*)/H(3); H(16)/H(21β); H(18)/H(21α); H(21α)/H(18); H(21β)/H(16); H(22a)/NH'; H(2')/NH', H(6'β), H(22'a); H(3')/H(9'); H(6'α)/H(9'); H(6'β)/H(2'); H(9')/H(3'), H(6'α); H(15')/H(18'), H(22'b); H(18')/H(15'); H(19')/H(22'b); H(22'a)/H(2'); H(22'b)/H(15'), H(18'), H(19'); NH'/H(22a), H(2'). NOE: H(3)/H(9), H(14*R*), H(14*S*), H(21α); H(6β)/H(6α); H(12)/H(22'a); H(15)/H(14*R*), H(14*S*), H(18), H(20), H(22b); H(21β)/H(16), H(21α); H(22a)/H(22b); H(22b)/H(15), H(16), H(22a); H(2')/NH', H(6'β), H(22'a); H(9')/H(3'); H(10')/H(9'), H(11'); H(14'*S*)/H(14'*R*); H(21'β)/H(21'α); H(22'a)/H(12), H(2'), H(22'b); H(22'b)/H(15'), H(22'a); NH'/H(2').

Tetrahydroalstonine (43): colorless oil; $[\alpha]_D$ −53 (*c* 0.10, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.31), 247 (3.77), 282 (3.64), 291 (3.49) nm; IR (dry film) ν_{max} 3370, 1703 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.29 and 2.30, respectively; ESIMS *m*/*z* 353 (MH^+, $C_{21}H_{24}N_2O_3$ + H).

17(*S*)-Ajmalicinial (44) and 17(*R*)-Ajmalicinial (45): light yellowish oil; IR (dry film) ν_{max} 3410, 3274 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.29 and 2.30, respectively; ESIMS *m*/*z* 313 (MH^+, $C_{19}H_{24}N_2O_2$ + H).

Akuammidine (46): colorless crystals ($CHCl_3$-MeOH); mp 250–252 ^oC; $[\alpha]_D$ +25 (*c* 0.10, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.18), 282 (3.51), 291 (3.39) nm; IR (dry film) ν_{max} 3261, 1714 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.31 and 2.32, respectively; ESIMS *m*/*z* 353 (MH^+, $C_{21}H_{24}N_2O_3$ + H).

16(*R*)-19,20-*E*-Isositsirikine (47): light yellowish oil; $[\alpha]_D$ −21 (*c* 0.05, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.27), 286 (3.96), 295 (3.65) nm; ^1H NMR and ^{13}C NMR data, see Tables 2.31 and 2.32, respectively; ESIMS *m*/*z* 355 (MH^+, $C_{21}H_{26}N_2O_3$ + H).

16(*S*)-19,20-*E*-Isositsirikine (48): light yellowish oil; $[\alpha]_D$ −77 (*c* 0.10, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.51), 282 (3.88), 318 (3.42) nm; ^1H NMR and ^{13}C NMR data, see Tables 2.31 and 2.32, respectively; ESIMS *m*/*z* 355 (MH^+, $C_{21}H_{26}N_2O_3$ + H).

***Z*-Geissoschizol (49):** light yellowish oil; $[\alpha]_D$ –42 (*c* 0.06, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (3.19), 224 (3.22), 281 (2.60) nm; IR (dry film) ν_{max} 3252 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.33; ESIMS *m*/*z* 297 (MH^+, $C_{19}H_{24}N_2O$ + H).

Fluorocarpamine (50): light yellowish oil; $[\alpha]_D$ +243 (*c* 1.64, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 232 (4.15), 260 (3.59), 289 (3.20) nm; IR (dry film) ν_{max} 1748, 1696 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.33; ESIMS *m*/*z* 339 (MH^+, $C_{20}H_{22}N_2O_3$ + H).

Pleiocarpamine (51): colorless oil; $[\alpha]_D$ +87 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (4.32), 284 (3.85) nm; IR (dry film) ν_{max} 1758 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.34; ESIMS *m*/*z* 323 (MH^+, $C_{20}H_{22}N_2O_2$ + H).

16-Hydroxymethylpleiocarpamine (52): light yellowish oil; $[\alpha]_D$ +102 (*c* 0.21, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.20), 284 (3.71) nm; IR (dry film) ν_{max} 3326, 1734 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.34; ESIMS *m*/*z* 353 (MH^+, $C_{21}H_{24}N_2O_3$ + H).

(–)-Isovallesiachotamine (53): light yellowish oil; $[\alpha]_D$ –63 (*c* 0.25, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 223 (3.86), 290 (3.80), 362 (2.40) nm; IR (dry film) ν_{max} 3306, 1670, 1613 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.35; EIMS *m*/*z* 350 (M^+, $C_{21}H_{22}N_2O_3$).

(–)-Isovallesiachotamine (53) and (+)-Vallesiachotamine (54): light yellowish oil; IR (dry film) ν_{max} 3306, 1670, 1613 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.35; EIMS *m*/*z* 350 (M^+, $C_{21}H_{22}N_2O_3$).

Norfluorocurarine (55): colorless crystals (acetone); mp 181–183 ^{o}C; $[\alpha]_D$ –900 (*c* 0.32, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 232 (4.27), 296 (3.86), 364 (4.33) nm; IR (dry film) ν_{max} 3298, 1643 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.36; EIMS *m*/*z* 292 (M^+, $C_{19}H_{20}N_2O$).

12-Hydroxynorfluorocurarine (56): light yellowish oil; $[\alpha]_D$ –645 (*c* 0.06, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 215 (4.09), 236 (3.86), 292 (3.19), 379 (3.72) nm; IR (dry film) ν_{max} 3294, 1642 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.36; ESIMS *m*/*z* 309 (MH^+, $C_{19}H_{20}N_2O_2$ + H).

Tubotaiwine (57): light yellow oil; $[\alpha]_D$ +609 (*c* 0.19, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.43), 231 (3.82), 295 (3.57) nm; IR (dry film) ν_{max} 3361, 1673 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.37 and 2.38, respectively; ESIMS *m*/*z* 325 (MH^+, $C_{20}H_{24}N_2O_2$ + H).

Tubotaiwine *N*-oxide (58): light yellowish oil; $[\alpha]_D$ +360 (*c* 0.04, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 201 (4.05), 229 (4.03), 294 (3.76), 327 (3.81) nm; IR (dry film) ν_{max} 3373,

1679 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.37 and 2.38, respectively; ESIMS *m*/*z* 341 (MH^+, $C_{20}H_{24}N_2O_3$ + H).

***N*(4)-Chloromethyltubotaiwine chloride (59):** light yellowish oil; $[\alpha]_D$ +323 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (3.89), 293 (3.75), 329 (3.84) nm; IR (dry film) ν_{max} 3353, 1681 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.37 and 2.38, respectively; LSIMS *m*/*z* 373 (M^+, $C_{21}H_{26}ClN_2O_2^+$); ESIMS *m/z* 373 $[M]^+$; HRESIMS *m/z* 373.1677 (calcd for $C_{21}H_{26}ClN_2O_2^+$, 373.1683).

Venoterpine (60): light yellowish oil; $[\alpha]_D$ –2 (*c* 0.11, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (3.62), 259 (3.07), 266 (2.98) nm; IR (dry film) ν_{max} 3350 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2.39; ESIMS *m*/*z* 150 (MH^+, $C_9H_{11}NO$ + H).

Syringaresinol (61): colourless oil; $[\alpha]_D$ +9 (*c* 0.07, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 237 (3.85), 272 (3.16), 280 (3.09) nm; IR (dry film) ν_{max} 3408 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2.39; EIMS *m*/*z* 418 (M^+, $C_{22}H_{26}O_8$).

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Compound 62: yellowish oil; $[\alpha]_D$ +72 (*c* 0.87, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 246 (3.86), 271 (3.68), 326 (3.11) nm; IR (dry film) ν_{max} 3304, 1722, 1665 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.41; ESIMS *m*/*z* 355 $[MH]^+$; HRESIMS *m*/*z* 355.2021 (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2016). HMBC: ^{2}J H(16) to C(2); H(6) to C(7); H(3) to

C(14); H(17) to C(16); H(18) to C(19); H(23) to C(22); H(22) to C(23). ^{3}J H(17) to C(2); H(22) to C(5); H(6), H(10) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(17), H(19) to C(15); H(19) to C(17); H(18) to C(20); H(3), H(6), H(15), H(17), H(19) to C(21). NOE: H(6)/H(9); H(9)/H(6), H(10); H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11); H(18)/H(19); H(19)/H(18); H(22)/H(23); H(23)/H(22).

Compound 63: light yellowish oil; $[\alpha]_D$ −5 (*c* 0.10, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 228 (4.60), 276 (3.93) nm; IR (dry film) ν_{max} 2852, 2796, 2739 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.42; ESIMS *m*/*z* 295 $[MH]^+$; HRESIMS *m*/*z* 295.1811 (calcd for $C_{19}H_{22}N_2O$ + H, 295.1805). HMBC: ^{2}J H(21) to C(2); H(6) to C(5); H(5) to C(6); H(6) to C(7); H(15) to C(14); H(14) to C(15); H(18) to C(19); H(21) to C(20). ^{3}J H(6), H(16) to C(2); H(15) to C(3); H(3), H(21) to C(5); H(5), H(21) to C(7); H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(19) to C(15); H(19) to C(16); H(21) to C(17); H(16), H(17), H(21) to C(19); H(18) to C(20); H(3), H(5), H(17), H(19) to C(21). NOESY: H(9)/H(10); H(10)/H(9); H(12)/H(16); H(15α)/H(19); H(15β)/H(19); H(16)/H(12), H(17); H(17β)/H(16); H(18)/H(19), H(21); H(19)/H(15α), H(15β), H(18); H(21)/H(18). NOE: H(16)/H(9), H(17α), H(17β); H(18)/H(19), H(21); H(19)/H(15α), H(15β), H(17β), H(18); H(21)/H(18).

Compound 64: light yellowish oil and subsequently light yellowish crystals from CH_2Cl_2–MeOH; mp 190–192 °C; $[\alpha]_D$ +381 (*c* 0.16, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.25), 234 (4.55), 257 (3.96), 308 (3.36), 376 (3.40) nm; IR (dry film) ν_{max} 2799,

2855, 1610 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.42; ESIMS *m*/*z* 311 $[MH]^{+}$; HRESIMS *m*/*z* 311.1756 (calcd for $C_{19}H_{22}N_2O_2$ + H, 311.1754). HMBC: ^{2}J H(6) to C(2); H(6) to C(5); H(5) to C(6); H(10) to C(11); H(15) to C(14); H(14) to C(15); H(17) to C(16); H(16) to C(17); H(18) to C(19); H(15), H(17), H(19) to C(20). ^{3}J H(5), H(16) to C(2); H(5), H(15) to C(3); H(21) to C(5); H(6), H(9), H(21) to C(7); H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(3), H(17), H(19) to C(15); H(15), H(21) to C(17); H(16), H(17) to C(19); H(14), H(16), H(18) to C(20); H(3), H(5), H(6), H(15), H(17), H(19) to C(21). NOE: H(3)/H(3), H(5), H(14), H(21); H(5)/H(3), H(5); H(6))/H(5); H(9)/H(10); H(10)/H(9); H(11)/H(12); H(12)/H(11), H(16); H(14)/H(3), H(15); H(15)/H(14), H(19); H(16)/H(17); H(17α)/H(16), H(17β), H(19); H(17β)/H(16), H(17α); H(18)/H(19), H(21); H(19)/H(15), H(17α), H(18); H(21)/H(3), H(18).

Larutenine (65): light yellowish oil; $[\alpha]_D$ 0 (*c* 0.03, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 207 (4.17), 228 (4.25), 275 (3.64), 292 (3.55), 356 (3.21) nm; ^{1}H NMR and ^{13}C NMR data, see Table 2.43; EIMS *m*/*z* 294 (M^{+}, $C_{19}H_{22}N_2O$).

(+)-19-Oxoeburnamine (66): light yellowish oil; $[\alpha]_D$ +83 (*c* 0.06, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (4.00), 282 (3.39), 292 (3.25) nm; ^{1}H NMR and ^{13}C NMR data, see Tables 2.44 and 2.45, respectively; EIMS *m*/*z* 310 (M^{+}, $C_{19}H_{22}N_2O_2$).

(–)-19(*R*)-Hydroxyisoeburnamine (67): yellowish oil; $[\alpha]_D$ −16 (*c* 0.18, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 203 (4.39), 229 (4.53), 282 (3.74), 292 (3.83) nm; ^{1}H NMR and ^{13}C NMR data, see Tables 2.44 and 2.45, respectively; EIMS *m*/*z* 312 (M^+, $C_{19}H_{24}N_2O_2$).

(+)-19(*R*)-Hydroxyeburnamine (68): light yellowish oil; $[\alpha]_D$ +111 (*c* 0.09, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 201 (3.86), 229 (4.02), 283 (3.42), 291 (3.31) nm; ^{1}H NMR and ^{13}C NMR data, see Tables 2.44 and 2.45, respectively; EIMS *m*/*z* 312 (M^+, $C_{19}H_{24}N_2O_2$).

Compound 69: light yellowish oil; $[\alpha]_D$ −13 (*c* 0.02, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (3.95), 253 (3.17), 284 (2.62) nm; IR (dry film) ν_{max} 3434, 2874, 2796, 1723, 1716 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.46 and 2.47, respectively; ESIMS *m*/*z* 353 $[MH]^+$; HRESIMS *m*/*z* 353.1863 (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1860). HMBC: ^2J H(14) to C(3); H(6) to C(5); H(5) to C(6); NH to C(13); H(14) to C(15); H(17) to C(16); H(19) to C(18); H(18) to C(19); H(21) to C(20). ^3J H(6) to C(2); H(5), H(21) to C(3); NH, H(9) to C(7); NH, H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(17), H(19), H(21) to C(15); H(21) to C(19); H(18) to C(20); H(5), H(19) to C(21); CO_2*Me*, H(17) to *C*O_2Me. NOESY: H(3)/H(14α), H(14β), H(15), H(21α); H(5α)/H(5β), H(6α), H(21α); H(5β)/H(5α), H(6β), H(9); H(6α)/H(5α), H(6β); H(6β)/H(5β); H(9)/H(5β), H(6β), H(10), H(14β); H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11); H(14α)/H(3), H(15); H(14β)/H(3), H(9), H(17a); H(15)/H(3), H(14α), H(18); H(17a)/H(17b),

H(14β); H(17b)/H(17a); H(18)/H(15), H(19); H(19)/H(18), H(21β); H(21α)/H(3), H(5α), H(21β); H(21β)/H(5β), H(19), H(21α).

Compound 70: light yellowish oil; $[\alpha]_D$ +38 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (3.97), 210 (4.04), 252 (3.51), 287 (2.81) nm; IR (dry film) ν_{max} 3227, 2801, 1720, 1713 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.46 and 2.47, respectively; ESIMS *m*/*z* 353 $[MH]^+$; HRESIMS *m*/*z* 353.1866 (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1860). HMBC: ^{2}J H(6) to C(5); H(5) to C(6); H(17) to C(16); H(19) to C(18); H(18) to C(19); H(21) to C(20). ^{3}J H(6) to C(2); H(5), H(21) to C(3); H(9) to C(7); NH, H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(17), H(19), H(21) to C(15); H(21) to C(19); H(18) to C(20); H(5), H(19) to C(21); CO_2Me, H(17) to CO_2Me. NOESY: H(3)/H(14α), H(14β); H(9)/H(10), H(14β); H(10)/H(9); H(11)/H(10), H(12); H(12)/H(11); H(14α)/H(3); H(14β)/H(3), H(9); H(15)/H(14β), H(18); H(17a)/H(17b), H(21α); H(17b)/H(17a); H(18)/H(15), H(19); H(19)/H(18), H(21β); H(21α)/H(3), H(5α), H(17a), H(21β); H(21β)/H(19), H(21α). NOE: H(3)/H(14β), H(21α); H(5α)/H(5β), H(21α); H(5β)/H(5α), H(6α), H(6β); H(6α)/H(6β); H(6β)/H(6α), H(9); H(9)/H(6β), H(10); H(12)/NH, H(11); H(15)/H(14β), H(18); H(17a)/H(17b), H(21α); H(17b)/H(17a); H(18)/H(15), H(19); H(19)/H(18), H(21β); H(21α)/H(3), H(5α), H(17a), H(21β); H(21β)/H(19), H(21α); NH/H(12).

Compound 71: light yellowish oil; $[\alpha]_D$ +42 (*c* 0.41, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (3.49), 251 (2.93), 291 (2.43) nm; IR (dry film) ν_{max} 3214, 2874, 2795, 1716 cm^{-1};

^{1}H NMR and ^{13}C NMR data, see Tables 2.46 and 2.47, respectively; ESIMS *m*/*z* 353 $[MH]^{+}$; HRESIMS *m*/*z* 353.1869 (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1860). HMBC: ^{2}J H(6) to C(5); H(5) to C(6); H(17) to C(16); H(19) to C(18); H(18) to C(19); H(21) to C(20). ^{3}J H(6) to C(2); H(5), H(21) to C(3); H(9) to C(7); NH, H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(17), H(19), H(21) to C(15); H(21) to C(19); H(18) to C(20); H(5), H(19) to C(21); CO_2*Me*, H(17) to *C*O_2Me. NOESY: H(3)/H(9), H(14β); H(5α)/H(3), H(21α); H(6α)/H(9); H(9)/H(3), H(6α), H(10); H(10)/H(9); H(11)/H(10), H(12); H(12)/H(11); H(14β)/H(3); H(15)/H(14α), H(14β), H(18); H(17a)/H(17b), H(21α); H(17b)/H(17a); H(18)/H(15), H(19); H(19)/H(18), H(21β); H(21α)/H(3), H(5α), H(17a); H(21β)/H(19). NOE: H(5α)/H(5β); H(5β)/H(5α); H(6α)/H(6β); H(9)/H(3), H(6α), H(10); H(11)/H(10); H(12)/H(11); H(14α)/H(14β); H(15)/H(14α), H(14β), H(18); H(17a)/H(17b), H(21α); H(17b)/H(17a); H(18)/H(15), H(19); H(19)/H(18), H(21β); H(21α)/(21β); H(21β)/H(19), H(21α).

(–)-Catharinensine (72): light yellowish oil; $[\alpha]_D$ –6 (*c* 0.05, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (3.61), 251 (3.17), 288 (2.49) nm; IR (dry film) ν_{max} 3277, 2874, 2796, 1720, 1711 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.48; ESIMS *m*/*z* 355 $[MH]^{+}$; HRESIMS *m*/*z* 355.2023 (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2016). HMBC: ^{2}J H(14) to C(3); H(6) to C(5); H(5) to C(6); NH to C(13); H(17) to C(16); H(19) to C(18); H(18) to C(19); H(21) to C(20). ^{3}J H(6) to C(2); H(5), H(6), H(21) to C(3); H(9) to C(7); NH, H(6), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(17), H(19), H(21) to C(15); H(21) to C(19); H(18) to C(20); H(3), H(5) to C(21); CO_2*Me*, H(17) to *C*O_2Me. NOESY: H(3)/H(15), H(21α);

H(5α)/H(21α); H(6β)/H(9); H(9)/H(6β), H(10); H(10)/H(9); H(11)/H(12); H(12)/NH, H(11); H(15)/H(3), H(21α); H(17a)/H(17b); H(17b)/H(17a); H(18)/H(20), H(21β); H(20)/H(18); H(21α)/H(3), H(5α), H(15); H(21β)/H(18); NH/H(12).

Tetrahydroalstonine pseudoindoxyl (73): light yellowish oil; $[\alpha]_D$ −196 (*c* 0.16, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (3.76), 235 (3.92) nm; IR (dry film) ν_{max} 3351, 1703, 1621 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.49; ESIMS *m*/*z* 369 $[MH]^+$; HRESIMS *m*/*z* 369.1803 (calcd for $C_{21}H_{24}N_2O_4$ + H, 369.1809). HMBC: ^2J H(14) to C(3); H(6) to C(5); H(5) to C(6); H(17) to C(16); H(18) to C(19); H(21) to C(20). ^3J H(5) to C(2); H(5), H(21) to C(3); H(3), H(6), H(9) to C(7); H(10) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(17), H(21) to C(15); H(17) to C(19); H(18) to C(20); CO_2Me, H(17) to CO_2Me. NOE: H(3)/H(15); H(5β)/H(5α); H(6β)/NH; H(9)/H(10); H(10)/H(9); H(11)/H(12); H(12)/NH, H(11); H(14α)/H(15); H(14β)/H(19); H(15)/H(3), H(14α), H(20), H(21α); H(18)/H(20), H(21β); H(19)/H(14β), H(18); H(20)/H(15), H(18), H(21α), H(21β); H(21α)/H(20), H(21β); H(21β)/H(18), H(21α); NH/H(6β), H(12).

(+)-Aspidospermidine (74): light yellowish oil; $[\alpha]_D$ +19 (*c* 0.05, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (3.75), 245 (3.35), 297 (2.98) nm; IR (dry film) ν_{max} 3361 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.50 and 2.51, respectively; ESIMS *m*/*z* 283 (MH^+, $C_{19}H_{26}N_2$ + H).

(+)-1,2-Dehydroaspidospermidine (75): light yellowish oil; $[\alpha]_D$ +148 (*c* 0.37, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 222 (4.50), 263 (3.85) nm; IR (dry film) ν_{max} 1579 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.50 and 2.51, respectively; ESIMS *m*/*z* 281 (MH^+, $C_{19}H_{24}N_2$ + H).

(–)-Quebrachamine (76): light yellowish oil; $[\alpha]_D$ –180 (*c* 0.19, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (3.45), 289 (2.82) nm; IR (dry film) ν_{max} 3191 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.50 and 2.51, respectively; ESIMS *m*/*z* 283 (MH^+, $C_{19}H_{26}N_2$ + H).

11,12-Dimethoxykopsinaline (77): light yellowish oil; $[\alpha]_D$ –18 (*c* 0.11, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (3.92), 250 (3.23), 293 (3.14) nm; IR (dry film) ν_{max} 3490, 3349, 1733 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.52; ESIMS *m*/*z* 415 $[MH]^+$; HRESIMS *m*/*z* 415.2220 (calcd for $C_{23}H_{30}N_2O_5$ + H, 415.2227). HMBC: ^2J H(18) to C(2); H(6) to C(5); H(5) to C(6); H(6), H(21) to C(7); H(10) to C(11); NH to C(13); H(17) to C(16); H(17) to C(20). ^3J H(6) to C(2); H(5) to C(3); H(21) to C(6); NH, H(9) to C(7); NH, H(10) to C(8); 11-OMe, H(9) to C(11); 12-OMe, H(10) to C(12); H(9) to C(13); H(17) to C(15); H(18) to C(16); H(15), H(19) to C(17); H(17) to C(19); H(18) to C(20); H(5), H(17) to C(21); CO_2Me, H(17) to CO_2Me.

Pseudokopsinine (78): light yellowish oil; $[\alpha]_D$ –20 (*c* 0.22, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.16), 245 (3.87), 295 (3.49) nm; IR (dry film) ν_{max} 3367, 1728 cm^{-1}; ^1H

NMR and ^{13}C NMR data, see Tables 2.53 and 2.54, respectively; ESIMS *m*/*z* 339 (MH^+, $C_{21}H_{26}N_2O_2$ + H).

Kopsinine (79): colorless oil; $[\alpha]_D$ −68 (*c* 0.24, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (4.56), 246 (3.88), 296 (3.48) nm; IR (dry film) ν_{max} 3350, 1728 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.53 and 2.54, respectively; ESIMS *m*/*z* 339 (MH^+, $C_{21}H_{26}N_2O_2$ + H).

Kopsamine (80): colorless crystals ($CHCl_3$–Et_2O); mp 200–201 ^oC; $[\alpha]_D$ –47 (*c* 0.21, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.36), 248 (3.92), 286 (2.92) nm; IR (dry film) ν_{max} 3315, 1736, 1684 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.55; ESIMS *m*/*z* 457 (MH^+, $C_{24}H_{28}N_2O_7$ + H).

***N*(1)-Decarbomethoxykopsamine (81):** colorless oil; $[\alpha]_D$ –9 (*c* 0.19, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 221 (4.65), 244 (4.11), 282 (3.39) nm; IR (dry film) ν_{max} 3452, 3349, 1727 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.55; ESIMS *m*/*z* 399 (MH^+, $C_{22}H_{26}N_2O_5$ + H).

Kopsilongine (82): colorless oil; $[\alpha]_D$ –21 (*c* 0.09, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 217 (4.34), 254 (3.92), 288 (3.20) nm; IR (dry film) ν_{max} 3318, 1737, 1675 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.56; ESIMS *m*/*z* 443 (MH^+, $C_{24}H_{30}N_2O_6$ + H).

Paucifinine (83): light yellowish oil; $[\alpha]_D$ –91 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.51), 248 (4.08), 255 (4.03), 285 (3.13), 290 (3.09) nm; IR (dry film) ν_{max} 3302, 1733, 1681 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.56; EIMS *m*/*z* 472 (M^+, $C_{24}H_{28}N_2O_8$).

Kopsanone (84): colorless oil; $[\alpha]_D$ +126 (*c* 0.20, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 207 (4.38), 244 (3.84), 294 (3.50) nm; IR (dry film) ν_{max} 3336, 1738 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.57; ESIMS *m*/*z* 323 (MH^+, $C_{20}H_{22}N_2O$ + H).

11,12-Methylenedioxykopsine (85): colorless oil; $[\alpha]_D$ –13 (*c* 0.18, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.61), 244 (4.24), 287 (3.41), 294 (3.39) nm; IR (dry film) ν_{max} 3310, 1756, 1684 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.58; EIMS *m*/*z* 424 (M^+, $C_{23}H_{24}N_2O_6$).

12-Methoxykopsine (86): colorless oil; $[\alpha]_D$ +310 (*c* 0.11, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 215 (4.58), 244 (4.05), 289 (3.52) nm; IR (dry film) ν_{max} 3422, 1727 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.58; EIMS *m*/*z* 410 (M^+, $C_{23}H_{26}N_2O_5$).

Kopsifine (87): colorless oil; $[\alpha]_D$ +97 (*c* 0.04, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 223 (4.41), 250 (3.94), 285 (3.16), 295 (3.10) nm; IR (dry film) ν_{max} 3295, 1765, 1684 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.59; EIMS *m*/*z* 438 (M^+, $C_{23}H_{22}N_2O_7$).

***N*(1)-Decarbomethoxykopsifine (88):** colorless oil; $[\alpha]_D$ +52 (*c* 0.07, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 220 (4.72), 243 (4.23), 288 (3.51) nm; ^{1}H NMR and ^{13}C NMR data, see Table 2.59; EIMS *m*/*z* 380 (M^+, $C_{21}H_{20}N_2O_5$).

Akuammicine (89): light yellowish oil; $[\alpha]_D$ −466 (*c* 0.07, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (3.74), 298 (3.68), 328 (3.83) nm; ^{1}H NMR and ^{13}C NMR data, see Table 2.60; ESIMS *m*/*z* 323 (MH^+, $C_{20}H_{22}N_2O_2$ + H).

Andransinine (90): light yellowish oil and subsequently light yellowish crystals from CH_2Cl_2-hexanes; mp 186–190 °C; $[\alpha]_D$ 0 (*c* 0.15, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 224 (3.99), 283 (3.36) nm; IR (dry film) ν_{max} 3391, 2885, 2840, 1727 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.61; ESIMS *m*/*z* 381 $[MH]^+$; HRESIMS *m*/*z* 381.2178 (calcd for $C_{23}H_{28}N_2O_3$ + H, 381.2173). HMBC: ^2J NH to C(2); H(6) to C(5); H(6) to C(7); NH to C(13); H(14) to C(15); H(17) to C(16); H(17), H(19) to C(18); H(23) to C(22); H(22) to C(23). ^3J H(6), H(21) to C(2); H(5), H(15) to C(3); NH, H(5), (9) to C(7); NH, H(6), H(10) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(19), H(22) to C(15); H(19) to C(17); H(17) to C(19); H(14) to C(20); H(3), H(5), H(15), H(17), H(19) to C(21); CO_2*Me*, H(21) to *C*O_2Me. NOE: H(3α)/H(3β); H(5β)/H(5α); H(6α)/H(6β), H(9); H(6β)/H(6α); H(12)/NH; H(15)/H(19); H(21)/H(3β), H(6β), H(22), H(23); H(22)/H(3β), H(15), H(19), H(21); H(23)/H(21), H(22).

Crystallographic data of 90: colorless block crystals, $C_{23}H_{28}N_2O_3$, *M*r = 380.47, monoclinic, space group $P2_1$, *a* = 8.5064(2) Å, *b* = 9.1496(2) Å, *c* = 12.5255(2) Å; $\alpha = \gamma = 90^o$, $\beta = 96.007(10)^o$, *V* = 969.51(3) $Å^3$, *T* = 100 K, *Z* = 2, D_{calc} = 1.303 gcm^{-3}, crystal size 0.17 x 0.21 x 0.44 mm^3, *F*(000) = 408. The final R_1 value is 0.0302 (wR_2 = 0.0774) for 2259 reflections [$I > 2\sigma(I)$].

Compound 91: light yellowish oil; $[\alpha]_D$ 0 (*c* 0.03, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 224 (4.03), 283 (3.43) nm; IR (dry film) ν_{max} 3384, 2840, 2818, 1727 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.61; ESIMS *m*/*z* 367 $[MH]^+$; HRESIMS *m*/*z* 367.2018 (calcd for $C_{22}H_{26}N_2O_3$ + H, 367.2016). HMBC: ^2J NH to C(2); H(6) to C(5); H(6) to C(7); NH to C(13); H(14) to C(15); H(17) to C(16); H(17), H(19) to C(18). ^3J H(6), H(21) to C(2); H(5), H(15) to C(3); NH, H(5), H(9) to C(7); NH, H(6), H(10) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); 15-OMe, H(19) to C(15); H(19) to C(17); H(17) to C(19); H(14) to C(20); H(3), H(5), H(15), H(17), H(19) to C(21); CO_2*Me*, H(21) to *C*O_2Me. NOE: H(3α)/H(3β); H(5α)/H(5β); H(6α)/H(6β); H(6β)/H(6α); H(9)/H(10); H(12)/NH, H(11); H(15)/CO_2*Me*; H(19)/15-OMe; 15-OMe/H(19).

Condylocarpine (92): colorless oil; $[\alpha]_D$ +619 (*c* 0.13, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.03), 296 (3.84), 329 (3.95) nm; IR (dry film) ν_{max} 3363, 1673 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.62; ESIMS *m*/*z* 323 (MH^+, $C_{20}H_{22}N_2O_2$ + H).

Precondylocarpine (93): light yellowish oil; $[\alpha]_D$ +407 (*c* 0.10, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.32), 296 (4.12), 329 (4.25) nm; IR (dry film) ν_{max} 3386, 1733 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.63; ESIMS *m*/*z* 353 (MH^+, $C_{21}H_{24}N_2O_3$ + H).

Stemmadenine (94): light yellowish oil and subsequently light yellowish crystals; mp 187–190 ^oC; $[\alpha]_D$ +270 (*c* 0.14, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (4.43), 228 (4.64), 287 (3.95) nm; IR (dry film) ν_{max} 3339, 1720 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2.63; ESIMS *m*/*z* 355 (MH^+, $C_{21}H_{26}N_2O_3$ + H).

Methyl 11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (95): colorless oil; $[\alpha]_D$ +89 (*c* 0.06, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 215 (3.26), 248 (2.71), 285 (1.83) nm; ^1H NMR and ^{13}C NMR data, see Table 2.64; ESIMS *m*/*z* 397 (MH^+, $C_{22}H_{24}N_2O_5$ + H).

Methyl 11,12-methylenedioxychanofruticosinate (96): colorless oil; $[\alpha]_D$ +51 (*c* 0.26, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 202 (4.02), 226 (3.60), 278 (2.94) nm; ^1H NMR and ^{13}C NMR data, see Table 2.64; ESIMS *m*/*z* 455 (MH^+, $C_{24}H_{26}N_2O_7$ + H).

Methyl chanofruticosinate (97): light yellowish oil; $[\alpha]_D$ +97 (*c* 0.51, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (4.26), 237 (3.88), 280 (3.14) nm; ^1H NMR and ^{13}C NMR data, see Tables 2.65 and 2.66, respectively; ESIMS *m*/*z* 411 (MH^+, $C_{23}H_{26}N_2O_5$ + H).

Methyl *N*(1)-decarbomethoxychanofruticosinate (98): colorless oil; $[\alpha]_D$ +258 (*c* 0.07, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 202 (3.74), 235 (3.18), 292 (2.67) nm; ^{1}H NMR and ^{13}C NMR data, see Tables 2.65 and 2.66, respectively; ESIMS *m*/*z* 353 (MH^+, $C_{21}H_{24}N_2O_3$ + H).

Methyl 12-methoxychanofruticosinate (99): colorless oil; $[\alpha]_D$ +194 (*c* 0.18, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 214 (4.23), 247 (3.63), 287 (2.90) nm; IR (dry film) ν_{max} 1741, 1716 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.65 and 2.66, respectively; ESIMS *m*/*z* 441 (MH^+, $C_{24}H_{28}N_2O_6$ + H).

(–)-Norpleiomutine (100): light yellowish oil; $[\alpha]_D$ –49 (*c* 1.21, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (4.69), 229 (4.51), 255 (4.09), 287 (3.97), 293 (3.97) nm; IR (dry film) ν_{max} 3348, 1730 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.67; ESIMS *m*/*z* 617 (MH^+, $C_{40}H_{48}N_4O_2$ + H).

***Alkaloids from Penicillium* sp. (CDA p48.3)**

Compound 101: light yellowish oil; $[\alpha]_D$ –2 (*c* 0.24, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (3.36), 287 (3.49), 332 (3.13) nm; IR (dry film) ν_{max} 3368, 1738, 1679 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2.70 and 2.71, respectively; LSIMS *m*/*z* 308 $[MH]^+$; HRLSIMS *m*/*z* 308.1859 (calcd for $C_{17}H_{25}NO_4$ + H, 308.1856). HMBC: ^2J H(3) to C(2); H(4) to C(3); H(3), H(5) to C(4); H(4) to C(5); H(7) to C(6); H(8) to C(7); H(7) to C(8); H(10) to C(9); H(10), H(18) to C(11); H(14) to C(13); H(14), H(16) to C(15); H(17) to C(16); H(16) to C(17). ^3J H(4), H(5) to C(2); H(5) to C(3); H(3) to C(5); H(8)

to C(6); H(10) to C(8); H(12), H(18) to C(10); H(9) to C(11); H(10), H(18) to C(12); H(12), H(16) to C(14); H(17) to C(15); H(10), H(12) to C(18).

Compound 102: light yellowish oil; $[\alpha]_D$ −6 (*c* 0.04, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 283 (3.46) nm; IR (dry film) ν_{max} 3385, 1726, 1659 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.70 and 2.71, respectively; LSIMS *m*/*z* 326 $[MH]^+$; HRLSIMS *m*/*z* 326.1962 (calcd for $C_{17}H_{27}NO_5$ + H, 326.1962). HMBC: ^2J H(3) to C(2); H(4) to C(3); H(3), H(5) to C(4); H(4) to C(5); H(7) to C(6); H(7) to C(8); H(10), H(18) to C(11); H(13) to C(12); H(15) to C(14); H(17) to C(16). ^3J H(4), H(5) to C(2); H(5) to C(3); H(3) to C(5); H(8) to C(6); H(10) to C(8); H(7) to C(9); H(18) to C(10); H(9), H(13) to C(11); H(18) to C(12); H(17) to C(15).

Compound 103: light yellowish oil; $[\alpha]_D$ +7 (*c* 0.09, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 289 (3.68) nm; IR (dry film) ν_{max} 3384, 1723, 1659 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2.70 and 2.71, respectively; LSIMS *m*/*z* 324 $[MH]^+$; HRLSIMS *m*/*z* 324.1809 (calcd for $C_{17}H_{25}NO_5$ + H, 324.1805). HMBC: ^2J H(3) to C(2); H(4) to C(3); H(3), H(5) to C(4); H(4) to C(5); H(7) to C(6); H(7) to C(8); H(10) to C(9); H(10), H(18) to C(11); H(16) to C(15); H(17) to C(16); H(16) to C(17). ^3J H(4), H(5) to C(2); H(5) to C(3); H(3) to C(5); H(8) to C(6); H(10) to C(8); H(7) to C(9); H(18) to C(10); H(9) to C(11); H(18) to C(12); H(16) to C(14); H(17) to C(15).

Variotin (104): light yellowish oil; $[\alpha]_D$ –6 (*c* 1.0, MeOH); UV (EtOH) λ_{max} (log ε) 320 (4.66) nm; IR (dry film) ν_{max} 3377, 1738, 1681 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.72; ESIMS *m*/*z* 292 (MH^+, $C_{17}H_{25}NO_3$ + H).

Viriditin (105): light yellowish oil; $[\alpha]_D$ –28 (*c* 0.35, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 206 (3.62), 273 (3.76) nm; IR (dry film) ν_{max} 3378, 1728, 1633 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.72; ESIMS *m*/*z* 308 (MH^+, $C_{18}H_{29}NO_3$ + H).

***cyclo* (L-Phenylalanine-*trans*-4-hydroxy-L-proline) (106):** light yellowish oil; $[\alpha]_D$ –104 (*c* 0.25, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 265 (2.85) nm; IR (dry film) ν_{max} 3378, 3249, 1659 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.73; ESIMS *m*/*z* 261 (MH^+, $C_{14}H_{16}N_2O_3$ + H).

***cyclo* (L-Leucine-*trans*-4-hydroxy-L-proline) (107):** light yellowish oil; $[\alpha]_D$ –99 (*c* 0.36, $CHCl_3$); IR (dry film) ν_{max} 3395, 3257, 1667 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2.73; ESIMS *m*/*z* 227 (MH^+, $C_{11}H_{18}N_2O_3$ + H).

3.9 Cytotoxicity Assays

Cytotoxicity assays were carried out on KB (human oral epidermoid carcinoma cell line), or Jurkat (human T-cell-leukemia cell line) cells. The cells were maintained in culture flasks in Eagle's MEM, supplemented with 10% fetal calf serum and kanamycin (60 μg/mL). The KB or Jurkat cells (1.5×10^5/mL) were seeded in 0.2 mL of culture medium/well in 96-well plates (Corning Glass Works). The cells were treated in triplicate with graded concentrations of 5 μL test samples and were then incubated in a 5% carbon dioxide atmosphere at 37 ℃ for 72 h. The MTT assay was used to measure the cytotoxicity effect.[409] The activity was shown as the IC_{50} value, which was the concentration (μg/mL) of test compound to give 50% inhibition of cell growth.

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